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Karolinska Institutet, Stockholm, Sweden

ELDERLY PATIENTS UNDERGOING COLORECTAL CANCER SURGERY – CAN CARE BE FURTHER IMPROVED?

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Karolinska Institutet

Stockholm 2017

Published by Karolinska Institutet.
Printed by Eprint AB 2017

ISBN 978-91-7676-570-8

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Research is formalized curiosity. It is poking and prying with a purpose. ”

Zora Neale Hurston

To my family.

ABSTRACT

Introduction: Colorectal cancer (CRC) is one of the most common malignancies affecting approximately 6 400 new patients/year in Sweden of which 44% are 75 years and older at diagnosis. In order to identify potential predictors for surgical outcome and areas of improvement, this thesis aims to illuminate different aspects in the care of patients aged 75 years and older, undergoing CRC surgery.

Methods: The studies in this thesis make use of a wide range of methods such as epidemiological methods: register based in study I and II, and prospective observational cohort study (IV). Qualitative methods with inductive content analysis were used in study III.

Aims and Results:

Study I investigated the characteristics of elderly colon cancer patients and how they are managed and treated compared to their younger counterparts when undergoing resection. Elderly patients were less often completely staged, and less often evaluated at a multidisciplinary team conference (MDT) prior to surgery. Furthermore, fewer elderly patients underwent curative resection and were more often subjected to emergency surgery.

Study II investigated if there is an association in elderly CRC patients between use of potentially inappropriate medication (PIM) at the time of surgery, and postoperative mortality and length of hospital stay (LOS). Results showed a significant association between use of PIM and increased postoperative mortality and LOS.

Study III investigated elderly CRC patients' experience of healthcare and the information given pre-, peri- and postoperatively. The results showed that feelings of vulnerability, uncertainty, disappointment, loss of control, and exposure were evident during the various phases of surgical care. This was the result of poor information about their cancer and planned treatment, potential impact on daily life and independency, as well as a negative perception of the hospital environment, need for support, and worries about the future. Rehabilitation was perceived as lacking individualisation, and persistent difficulties in regaining appetite and nutritional status prevented a quick recovery. Perception of unclear division of responsibility between care providers was evident after discharge.

Study IV investigated if geriatric risk factors identified by a comprehensive geriatric assessment (CGA) performed preoperatively could predict postoperative complications and LOS in elderly patients undergoing CRC surgery. Although no association was seen between the results of individual instruments used in the CGA and postoperative outcome, it was observed that elderly patients tolerated surgery well, and in general regained their preoperative functional status during the follow-up period.

Conclusions: Elderly patients are capable of recovering well from elective surgery but there are several areas for improvement. The results revealed age-dependent differences in the surgical care of CRC patients, to the disadvantage of older patients. PIM is associated with worsened outcome and elderly patients perceive the care and information received as lacking individual adaptations. We therefore believe that elderly patients could benefit from a thorough geriatric assessment prior to surgery in order to identify risk patients and adapt and improve peri-operative care in elderly CRC patients.

LIST OF SCIENTIFIC PAPERS

I. Egenvall M., Schubert Samuelsson K., Klarin I., Lökk J., Sjövall A., Martling, A., Gunnarsson U.
Management of colon cancer in the elderly: a population-based study.
Colorectal Dis. 2014 Jun;16(6):433-41. doi: 10.1111/codi.12575. PMID: 24460639

II. Schubert Samuelsson K., Egenvall M., Klarin I., Lökk J., Gunnarsson U.
Inappropriate drug use in elderly patients is associated with prolonged hospital stay and increased postoperative mortality after colorectal cancer surgery: a population-based study.
Colorectal Dis. 2016 Feb;18(2):155-62. doi: 10.1111/codi.13077. PMID: 26242564

III. Schubert Samuelsson K., Iwarzon M., Egenvall M., Klarin I., Lökk J., Gunnarsson U.
Elderly peoples' experiences of health care process and information when undergoing colorectal cancer surgery.
Submitted

IV. Schubert Samuelsson K., Egenvall M., Klarin I., Lökk J., Gunnarsson U.
Preoperative geriatric assessment and follow-up of patients 75 years and older undergoing colorectal cancer surgery.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ACCI	Age-Adjusted Charlson Comorbidity Index
ADL	Activity of Daily Living
ASA	American Society of Anesthesiologists
ATC	Anatomic Therapeutic Chemical Classification System
CAM	Confusion Assessment Method
CEA	Carcinoembryonic Antigen
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CRC	Colorectal Cancer
CT	Computed Tomography
DFRI	Downton Fall Risk Index
EQ-5D	EuroQol-5-Dimensions
ERAS®	Enhanced Recovery After Surgery
GDS-20	Geriatric Depression Scale-20
HRQoL	Health-related Quality of Life
LOS	Length of Stay in Hospital
MDT	Multidisciplinary Team Conference
MMSE	Mini-Mental Standard Examination
MNA-SF	Mini Nutrition Assessment-Short Form
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
OTC	Over-The-Counter Drugs
PIM	Potentially Inappropriate Medication
POD	Postoperative Delirium
SCRCR	The Swedish ColoRectal Cancer Register
SIOG	The International Society of Geriatrics
SD	Standard Deviation
The Board	The Swedish National Board of Health and Welfare (Socialstyrelsen)
TNM	Tumour Node Metastases
TRST	Triage Risk Screening Tool

1 INTRODUCTION

1.1 COLORECTAL CANCER

1.1.1 Epidemiology

Colorectal cancer (CRC) is the third most common cancer worldwide (9.7% of all cancer forms; 1.4 million new cases per year). The incidence varies across the world with the highest incidence in Western countries. In 2012, 694 000 persons died of CRC (8.5% of total cancer deaths), most occurring in poorly developed countries[1].

Even in Sweden, after prostate cancer and breast cancer, in men and women respectively, and skin cancer, CRC is the most common cancer form and accounts for approximately 6 400 new cases each year[2]. Between the years 1980 and 2014, the incidence of colon cancer increased slightly from 33 cases/100 000 inhabitants to 45 cases/100 000 inhabitants, whilst the incidence of rectal cancer remained essentially unchanged (20 cases in 1980 vs. 23 cases/100 000 inhabitants in 2014). Both colon cancer and rectal cancer have a higher incidence in men than in women. During the same time period, the mortality for colon cancer fell from 25 cases/100 000 inhabitants to 19 cases/100 000 inhabitants. For rectal cancer the mortality fell from 12 cases/100 000 inhabitants in 1980 to 8 cases/100 000 cases in 2011 (Figures 1a, 2a). The incidences of colon and rectal cancer increase with age (Figures 1b, 2b) illustrated by the fact that in 2014, 61% of Swedish CRC patients were 70 years and older, while 44% were 75 years and older at the time of diagnosis[2].

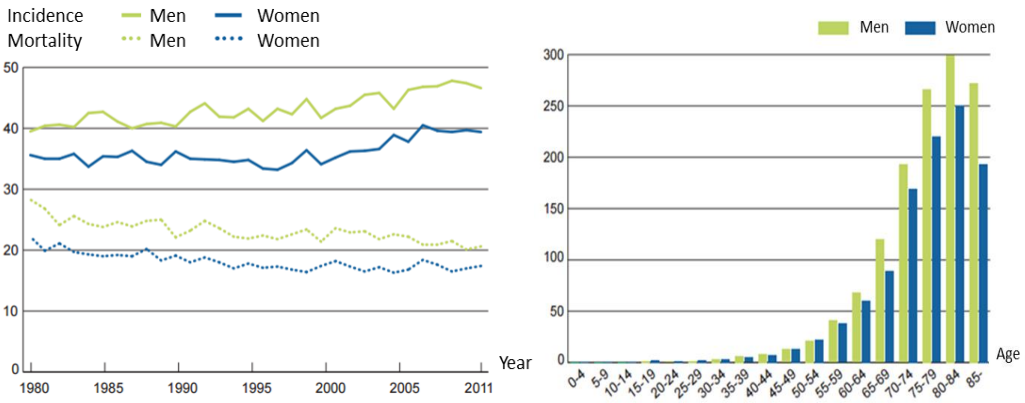

Figure 1. *Colon cancer.* ***a.*** *Age-standardised incidence and mortality/100 000 inhabitants 1980-2011 in Sweden.* ***b.*** *Incidence per 100 000 inhabitants in Sweden 2014 – presented as 5-year-age cohorts[3].*

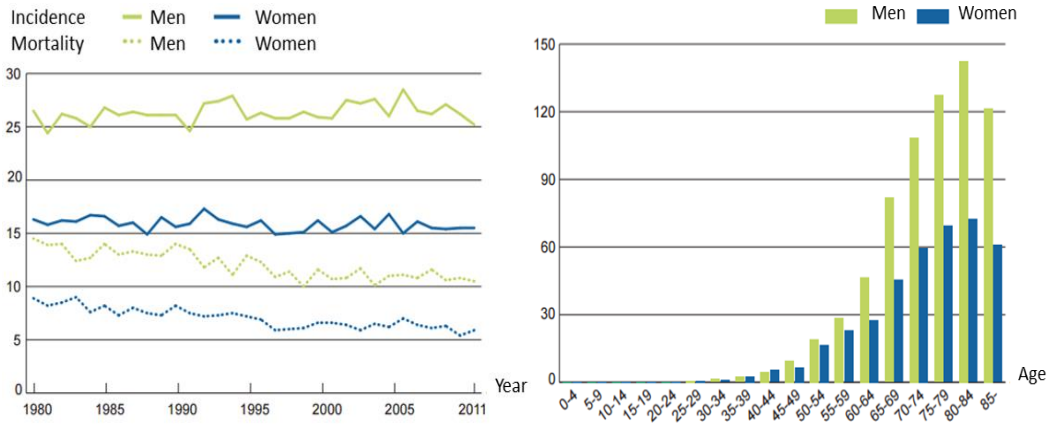

Figure 2. *Rectal cancer.* ***a.*** *Age-standardised incidence and mortality/100 000 inhabitants 1980-2011 in Sweden.* ***b.*** *Incidence per 100 000 inhabitants in Sweden 2014 – presented as 5-year-age-cohorts*[3].

The development of cancer begins with the transformation and clonal expansion of a single cell. Besides advanced age there are several extrinsic and intrinsic factors influencing the risk of occurrence of cancer. Environmental risk factors such as dietary and life-style factors might account for as much as 70-80% of all CRC cases[4]. This may partially be the reason for the irregular incidence distribution throughout the world. Genetic risk factors are associated with a family history of CRC or polyps, and a personal history of inflammatory bowel disease or adenomatous polyps all of which further increase the risk for CRC[4,5].

In Sweden, the National Board of Health and Welfare (Socialstyrelsen, the Board) recommends that screening for CRC every other year should be offered to all citizens between the ages of 60 and 74 years. The implementation of screening programmes is estimated to prevent the death of approximately 300 individuals due to CRC each year in Sweden[6].

1.1.2 Diagnosis

Upon diagnosis or suspicion of CRC, patients are referred to a surgical clinic for further investigation. Determination of the tumour stage is necessary for tailoring subsequent management. Staging includes assessment of local growth (T), lymph node metastasis (N), and distant metastasis (M) as well as several other descriptive parameters predictive of outcome (*e.g.* ingrowth in blood vessels etc.)[7].

First choice of examination methods of colon cancer are colonoscopy and computed tomography (CT) of the chest and abdomen. In cases of rectal cancer, digital rectal examination, rectoscopy, endorectal ultrasound and magnetic resonance imaging (MRI)[7] are performed for assessments of local tumour growth, and CT of the abdomen and chest for assessment of metastases. Biopsies should be obtained preoperatively via colonoscopy or rectoscopy for verification of malignancy. Despite lacking sensitivity for diagnostic purpose,

tumour markers such as CEA (carcinoembryonic antigen) are recommended preoperatively for staging, prognostic information[7] and for postoperative surveillance for both local recurrence and distant metastases[8].

1.1.3 Staging

Staging aims to describe tumour size, lymphatic involvement and presence of distant metastases using the TNM-classification[9]. The combination of these three parameters is used to describe the stage of the tumour (Table 1). Preliminary staging is performed using the preoperative clinical (c) assessment tools (*i.e.* radiology, biopsy) and is labelled "cTNM". After surgery, histopathologic (p) examination of the removed bowel specimen is performed and the resulting stage labelled "pTNM".

- T – Primary tumour size
- N – Regional lymph nodes (N0=0 and N2 if more than three positive lymph nodes)
- M – Metastases (0=no, 1=yes)
- X – not gradable or not investigated

Stage	TNM	Stage	TNM
0	Tis* N0 M0	IIIA	T1, T2 N1 M0
I	T1 N0 M0	IIIB	T3, T4 N1 M0
	T2 N0 M0	IIIC	Any T N2 M0
IIA	T3 N0 M0	IV	Any T, Any N, M1
IIB	T4 N0 M0		

Table 1. *TNM classification[9] and corresponding clinical staging. *Tis = carcinoma in situ (intra-epithelial cancer or invasion of Lamina propria)*

1.1.4 Multidisciplinary team conference

After completion of preoperative assessment and staging, each patient should be discussed at a MDT conference. In this forum, surgeons, specialised nurses, pathologists, radiologists and oncologists meet to decide on therapeutic options for colorectal cancer patients. Besides tumour stage, patient characteristics and comorbidity, other relevant factors are also taken into account prior to treatment decisions. MDT conferences have been shown to increase the use of chemotherapy and to be an independent predictor for cancer survival[10]. On the other hand, MDT conferences are time-consuming and costly and in routine cases treatment plans are usually just confirmed at a MDT conference, whereas in more complex

cases (*e.g*. rectal cancer, recurrence or metastasis) suggested management is more likely to be changed after a MDT conference[11].

1.1.5 Surgical Treatment

The definition of colon cancer is a cancer located more than 15 centimetres from the anal verge, while those below 15 centimetres are defined as a rectal cancer. CRC is classified as an adenocarcinoma.

1.1.5.1 Colon cancer

For early colon cancer, endoscopic excision is possible; otherwise left or right hemicolectomy is the primary treatment choice, aiming at complete removal of the tumour mass (*i.e.* removing all tumour mass including supplying vessels and corresponding regional lymph nodes, together with an intact mesentery)[7]. This procedure is called complete mesocolic excision and can achieve a radical result in almost all cases undergoing surgery with curative intent[12]. Open surgery is still standard practice, but more and more patients are operated laparoscopically, and the Board recommends that laparoscopy should be offered from the beginning[8]. In elderly colon cancer patients, laparoscopic surgery has been shown to reduce postoperative morbidity, shorten hospital stay, and enable rapid return to functional independency[13-15].

Most operations are performed on an elective basis, but approximately 20-25% are emergency procedures due to stenosis and subsequent bowel obstruction, perforation or bleeding[16]. Emergency procedures are furthermore associated with prolonged hospital stay and decreased survival[17].

1.1.5.2 Rectal cancer

In early stages, transanal excision or transanal endoscopic microsurgery may be performed. Otherwise, total mesorectal excision is the standard procedure aiming at the complete removal of the tumour mass, blood vessels, and regional lymph nodes including the mesenterium covered with an intact mesorectal fascia, thereby reducing the risk for recurrence. This technique has resulted in an increase in survival rates over the last two decades[18]. During recent years, minimally invasive laparoscopic surgery and robot-assisted surgery have evolved as alternative techniques in rectal cancer surgery[8].

1.1.5.3 Postoperative complications

Overall morbidity after surgery is seen in approximately 30% of the patients. Common non-surgical morbidity includes cardiac and pulmonary complications (frequency ranging from 0-7% and 0-11% respectively). Furthermore, urogenital, neurological, thromboembolic and renal complications do occur. The use of minimally invasive techniques may decrease the risk for complications after colon cancer surgery[19]. Surgical complications occur in approximately 20% of colorectal patients[20]. These include: anastomotic leakage, wound complications, obstruction, postoperative bleeding, intra-abdominal infection, and stoma complications. Postoperative 30-day mortality has an incidence of 3-6% after elective surgery but increases to 10-22% in emergency surgery[20].

1.1.6 Oncological treatment

In rectal cancer with higher risk for local recurrence, neoadjuvant radiotherapy is given prior to surgery. Short-course radiation aims to eradicate micrometastases in the surrounding tissues and thereby reduce the risk for recurrence. Subsequent surgery is performed within ten days. In more distally located or advanced rectal cancer, long-course radiation in combination with chemotherapy is used to decrease tumour mass with subsequent surgery within 6-8 weeks[8].

If lymph node metastasis is confirmed by pathology, or there are reasons to suspect risk for recurrence (*e.g.* extramural vascular, perineural or lymph vessel invasion into nearby structures, tumour deposits, perforation) adjuvant chemotherapy is added[8]. Very old patients with co-morbidity and decreased performance status are often excluded from adjuvant chemotherapy[21] due to concern about toxicity of the drugs used.

Approximately 20% of CRC patients have distant metastases at the time of diagnosis[22]. Due to the direct venous drainage from the bowel to the portal vein system, distant metastases commonly occur in the liver. Other metastatic sites are lung, ovary, and peritoneum. Surgery with curative intent can be possible even in the presence of distant metastases. If the primary tumour is radically resected, the 5-year survival rate after resection of liver metastases is 30-40%, and after resection of lung metastases 25-40%[23]. In most cases, neoadjuvant chemotherapy is applied with subsequent resection of metastases and the primary tumour, either in separate or synchronous procedures. In cases with peritoneal metastases, cancer resection can be combined with intraperitoneal administration of chemotherapy intraoperatively. This is a tough treatment given to patients under 75 years of age with limited carcinomatosis.

For unresectable stage IV CRC, palliative chemotherapy is available, but is not recommended for patients over 75 years[8].

1.1.7 Enhanced recovery after surgery

Under the late 90's, multimodal approaches, later named "enhanced recovery after surgery" (ERAS®), were developed, aiming to optimise perioperative management[24]. These programmes include preoperative, intraoperative, and postoperative elements of care aimed at reducing surgical stress and postoperative catabolism, thereby reducing postoperative complications and LOS[25]. Initially designed for colon surgery[26], programmes for rectal surgery were subsequently included in the evidence database in 2009[27]. The International ERAS® Society, based in Stockholm, Sweden, has assembled a database of knowledge that has spread worldwide[28].

Amongst other things, the ERAS® programme applies perioperative recommendations[29] addressing several problems frequently occurring in elderly patients:

- Mental preparation: preoperative information about planned treatment and course
- Malnutrition: preoperative carbohydrate loading instead of fasting, early enteral nutrition and nutritional support after surgery
- Risk of dehydration and electrolyte derangement: no routine bowel preparation
- Impaired mobility: no routine application of long- or short-acting sedative medication
- Postoperative delirium: epidural analgesia using local anaesthetics and low-dose opioids

Several studies have confirmed the benefits of ERAS®, but in most of these, elderly patients were excluded or not represented. A systematic review of 16 studies with CRC patients aged 65 years and older showed a shorter hospital stay and fewer complications when comparing an ERAS® to a non-ERAS® regimen (2 randomised controlled trials), while observational studies were inconsistent regarding LOS, mortality and morbidity when comparing ERAS® - patients older and younger than 65 years[30].

1.1.8 Survival

In 2011, the 5-year survival for colon and rectal cancer in Sweden was 65.5% and 63.6% respectively, and the 10-year survival was 60.1% and 56.0% respectively[3]. Not surprisingly, detection at an early cancer stage is one of the strongest predictors for survival[20] with a 5-year survival rate exceeding 90% for localised cancer, whereas the 5-year survival for patients with metastatic CRC hardly exceeds 10%[31]. Improved treatment of liver metastases

has had a positive influence on survival over recent years[32]. Negative predictors for CRC survival are comorbidity and emergency surgery[20].

Recurrence of CRC can occur as local recurrence and metastases. Furthermore, the risk for metachronous tumours is increased for patients with CRC. Surveillance is performed at 12- and 36-months follow-up after the index surgery and includes CEA, CT of the chest and abdomen. Colonoscopy is performed 3 years after the index tumour and thereafter every 5th year until the patients turn 75 years[8].

1.2 THE GERIATRIC POPULATION AND ITS SPECIAL CONCERNS

In an attempt to define the older age-group, the United Nations agreed to use 60 years and older as a chronological marker. However, the World Health Organization set 50 years[33], acknowledging situations in countries other than in the Western world. In Western countries, the definition of old age is moving upwards due to increasing life expectancy. It has become accepted that whether a person is judged to be old, is based not only on chronological but also biological and social factors.

1.2.1 Comorbidity, multimorbidity and frailty

As a group, the geriatric CRC population is heterogeneous consisting of both patients with excellent health status and others with comorbid conditions, loss of independency due to functional decline, and shortened life expectancy. The terms “comorbidity” and “multimorbidity” are often used to describe the same condition.

Comorbidity was originally defined as “an associated illness arising from other diseases”[34] but the term is also used in a broader sense throughout the literature. “Multimorbidity” refers to the coexistence of two or more acute or chronic medical conditions or diseases in the same individual[35]. A review including 41 articles showed a wide prevalence of multimorbidity in older persons (55 to 98%). Associated factors were older age, female sex, and low socioeconomic status. The major consequences of multimorbidity were disability and functional decline, poor quality of life, as well as high healthcare costs. Divergent results were found regarding the association between multimorbidity and mortality risk[36].

With increasing age, the incidence of disease increases, and physiological changes in the aging body contribute to a more fragile health condition. “Frailty” describes a state of increased vulnerability due to an age-associated decline in physiologic reserve and function across multiple organ systems. Although no consensus definition of frailty currently exists, frequent clinical presentations are fatigue, unexplained weight loss, frequent infections, balance and

gait impairment, delirium and fluctuating disability. Any sudden change in health status cannot be compensated, increasing the risk for adverse conditions – also called geriatric syndromes[37].

1.2.2 Geriatric syndromes

A geriatric syndrome describes a serious health condition occurring in elderly people that cannot be categorised in usual disease classification systems. Delirium, functional decline, falls, frailty, urinary incontinence, dizziness, syncope, and pressure ulcers are common geriatric syndromes which are associated with higher morbidity and disability and decreased quality of life. Geriatric syndromes are multifactorial but have risk factors in common; older age, cognitive and functional impairment, and impaired mobility[38].

1.2.3 Colorectal cancer surgery in the elderly patient

Regarding presenting cases at MDT conferences, patients with considerable comorbidity were less likely to be discussed, and comorbidity itself seemed to be insufficiently discussed when deciding about the most appropriate treatment[39]. High age *per se* was also identified as a potential reason not to present cases at MDT conferences[40].

Patients, aged 75 years and older, have a decreased survival rate after colorectal cancer surgery which is mainly due to a higher early mortality during the postoperative period[41]. In fact, if elderly patients survive the first postoperative year, cancer-related survival is comparable to that of younger patients[42]. This emphasises the importance of balanced and optimised perioperative care, planning of rehabilitation and follow-up during the first postoperative year.

In elective surgery for disseminated cancer, unintentional weight loss (more than 10% weight loss during the six months prior to surgery) has been shown to be a negative predictor for surgical outcome and is often associated with various comorbidities, leading to increased postoperative morbidity and mortality[43].

The impact of age seems to be ambiguous. In a study on 291 patients 80 years and older, age alone was not associated with increased 30- and 90-day mortality after elective surgery, whilst postoperative morbidity was associated with age[44]. Other studies have identified high age, emergency surgery, and neurological comorbidity[45], as well as concomitant heart and/or lung diseases[46] as having a negative impact on postoperative mortality and morbidity. Frailty was identified as an independent determinant for impaired postoperative outcome[47].

1.2.3.1 Postoperative complications and outcome in elderly patients

Common postoperative complications in elderly CRC patients are renal and wound complications[48] as well as infections, cardiac failure and death[46,48]. Death due to complications occurred more frequently than in younger patients[20]. When undergoing emergency surgery, the risk for postoperative morbidity and mortality is considerably higher[46].

An American register-based study on 939 150 patients aged 55 and above, who were admitted to the hospital for major cancer surgery 2009-2011, investigated the occurrence of geriatric events during hospital stay. In total, geriatric events occurred in 9.2%. Elderly patients (65 to 74 years) and very elderly patients (75 years and above) had a significantly higher risk for geriatric events as well as patients with higher comorbidity and those who underwent emergency surgery. Nutrition-related events (failure to recover, dehydration) occurred in 81.3%, delirium in 17.1%, and mobility-related events (pressure ulcer, falls, and fractures) occurred in 9.6%. Risk factors were: advanced age (75 years and older), higher comorbidity, emergency surgery, and admission to non-teaching institutions or low-volume centres. Patients who underwent surgery for colon and/or rectal cancer had one of the highest geriatric event rates, 16.6% (1.0% to 25.5% depending on cancer location). These were associated with prolonged hospitalisation, higher healthcare costs, as well as less likelihood to be discharged to home and a higher risk for mortality during the hospital period[49].

Postoperative delirium after colorectal surgery is a complication with significant consequences: higher incidence of non-surgical complications and mortality, prolonged LOS and more frequently discharge to a nursing home[50]. Frequency rates in elderly patients undergoing gastrointestinal surgery differ widely (8.2% to 54.4%) and identified risk factors are old age, history of alcohol excess, ASA class III or more, low body mass index, decreased serum albumin level, intraoperative hypotension, and perioperative blood transfusion[51]. In addition, greater comorbidity, cognitive impairment, increased disability, preoperative psychotropic drug use, depression, and previous POD were identified as risk factors[52].

In 2013, the International Society of Geriatric Oncology (SIOG) updated their recommendations from 2009 regarding management of CRC in older patients[53]. These recommendations include both surgical and oncologic treatments, and identify several areas of special consideration in these patients:

- Toxicity
- Completion of therapy

- Immediate postoperative mortality
- 30-day postoperative morbidity and mortality
- Length of hospital stay
- Discharge to nursing home
- One-year-mortality
- Short- and long-term functional outcomes and quality-of-life
- Progression
- Survival
- Composite end points (overall treatment utility)

Several recommendations from the SIOG regarding surgery aim to identify patients in need of involvement of a geriatrician in order to reduce comorbidity and frailty hazards. There are several tools available which provide the opportunity to screen for frailty[54]. Upon identifying a frail patient, a formal CGA should be considered. Furthermore, a prehabilitation programme should be initiated when malnutrition is discovered, or cardiovascular or pulmonary comorbidities are present, and a review of the patient's medication should be standard routine. For these patients, major resection surgery should be postponed in order to allow for optimisation, and emergency surgery should be avoided whenever possible. The importance of preoperative information given to the patient regarding risks and outcome is emphasised[53].

1.2.4 Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) is defined as a multidisciplinary process aimed to identify medical, psychosocial, and functional limitations of a frail elderly person, but is also used as a name for a set of tools used in the geriatric assessment process. Its aim is to identify individual weaknesses, strengths and resources that should be considered when planning individual care[55]. Essential points of interest are: functional status, nutrition, cognition, social support, mood, comorbidity, polypharmacy, and frailty[56]. Since there is a lack of agreement on which patients benefit from a CGA, usual patient criteria for performing a CGA are: high age, presence of comorbidity, geriatric conditions (*e.g.* falls, functional decline), frequent healthcare use, and change in social situation.

Inclusion of a geriatrician in the multidisciplinary team considering an elderly cancer patient, and the CGA performance have been shown to facilitate the identification of patients at risk for cognitive impairment, malnutrition, depression and frailty, as well as initiating cooperation between medical and paramedical healthcare professionals. This promotes improvement of symptom management and evaluation of medication use[57]. As treatment progresses, the geriatrician can help to identify early signs of a complication[58].

A review of six studies on elective surgery using different CGA approaches and subsequent interventions, came to the conclusion that there might be a positive impact on LOS and non-surgical postoperative complications, but that each study had flaws influencing the interpretation/quality of the data[59].

In an interesting study, SIOG asked cancer surgeons from the USA and EU about their attitudes to assessment and decision-making in older cancer patients. 90% of the responding surgeons did not regard chronological age as a contraindication to surgery whereas severely impaired cognitive status – regardless of full functional status – was considered by 51% to be a reason not to operate. Frailty and nutritional status were assessed by 48 and 38%, respectively. The majority did not use the expertise of a geriatrician at all. However, about 70% were positive to postpone surgery for preoperative optimisation when there was evidence that this would lead to improvement in functional recovery. When looking more closely at the different specialities, visceral surgeons were more prone to use a lower age threshold and to deny elective surgery because of high age. On the other hand, they were more open to the use of a preoperative CGA, frailty assessment and collaboration with a geriatrician[60].

1.2.5 Medication in the elderly patient

Both pharmacokinetic (*i.e.* how the body affects a drug) and pharmacodynamic (*i.e.* how a drug affects the body) changes occur in the aging human. Due to progressive structural and functional impairment of all organ systems, the homeostatic capacity is reduced, leading to increased vulnerability to stress. Changes in body composition (increased fat mass) and decline in renal and hepatic function will increase the distribution volume and reduce clearance of lipid-soluble drugs such as benzodiazepines, while water-soluble drugs tend to have a reduced distribution volume and reduced clearance. This results in prolonged plasma elimination and half-life with increased risk for accumulation and thus longer duration of drug effect. Pharmacodynamic changes in general lead to increased sensitivity (*e.g.* cardiovascular system) to drugs[61] and increased risk for adverse effects despite making adjustments to compensate for pharmacokinetic changes. A wide inter-individual variety of age-related changes adds to the complexity of pharmacological treatment in the elderly.

1.2.5.1 Polypharmacy

Increasing multimorbidity results in increased prescription of a wide range of medications in the elderly population. In recent decades, drug use has continued to increase to such an extent that the average number of medications is now 5 for community-dwelling older people and 8-10 for elderly persons in nursing homes[62]. Due to this increase in drug prescriptions, the

risk for adverse side-effects and drug-drug interactions increases, with potentially life-threatening consequences for elderly people. The incidence of drug-drug interactions vary widely in studies depending on study population and study settings. However, in a recent study, almost two thirds of patients aged 65 and older who were admitted to an emergency department had at least one potential drug-drug-interaction. In spite of this, only 9% of these drug-drug-interactions were actually the reason for admission[63]. Delirium, oversedation and falls are common adverse drug events occurring in older people as shown in a North American study of 1247 long-term care residents[64]. It should be noted that the majority of harm caused by these drugs can be avoided, and a systematic review including 26 studies has shown that drug reconciliation on a regular basis reduced the number of medication discrepancies with a corresponding reduction of potential and actual adverse drug reactions[65].

In the field of research, there are several definitions of polypharmacy. A common definition defines polypharmacy as the number of medications used on a daily base (*e.g.* 5 or more) while other definitions take into account the use of inappropriate medication or several drugs with similar effect[66].

1.2.5.2 Potentially inappropriate medication in elderly people

Potentially inappropriate medication (PIM) is defined as "medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available"[67]. PIM includes drugs with decreased tolerance due to age-related physiological changes, incorrect dosage, duration or indication, but even undertreatment is included here. A review from 2011 showed a prevalence of 12-63% inappropriate drug use in the elderly and was associated with female sex, advanced age and total number of drugs prescribed[68].

In 1991, Beers published implicit (*i.e.* use of clinical judgment and assessment of harm versus benefit in a patient-specific context) and explicit (*i.e.* the use of a list of medications or medical conditions) criteria regarding inappropriate medication[69] (latest update 2015[70]). This support tool is widely used in USA but about 50% of the medications listed are not used in Europe.

Revised versions suitable for use in European Countries were published in 2008: the STOPP/START criteria[71]. These acronyms stand for "Screening Tool of Older Persons' Prescriptions" (65 clinically significant indicators for potentially inappropriate prescription in elderly patients) respectively "Screening Tool to Alert doctors to Right Treatment" (22 evidence-based indicators for prescription omissions)[72].

The Swedish government assigned the Swedish National Board of Health and Welfare to develop quality indicators for evaluation of drug therapy in older patients. In 2004 and updated in 2010, the Board published both disease- and drug-specific indicators for appropriate drug use in older people based on international research, in order to give physicians support when improving the quality of pharmacotherapy for this particular patient group[62].

2 AIMS

General aim

The overall aim of this thesis was to describe various aspects of care of patients 75 years and older when undergoing colorectal cancer surgery and to identify targets for improvement.

Specific aims

Study I

To describe characteristics and management of patients 75 years and older undergoing resection for colon cancer and to compare these with younger patients.

Study II

To investigate the possible impact of intake of inappropriate medication at the time of colorectal cancer surgery on length of hospital stay and 30-day-postoperative mortality.

Study III

To describe how patients 75 years and older experience healthcare and information received prior to, during and after colorectal cancer surgery.

Study IV

To test if specific geriatric assessment instruments used preoperatively can predict postoperative outcomes such as postoperative complication and length of hospital stay in patients 75 years and older undergoing elective colorectal cancer surgery. A secondary aim was to investigate postoperative recovery during the first year using corresponding assessments.

3 METHODS

3.1 SETTINGS

3.1.1 The Swedish National Cancer Register

Founded in 1958, this nationwide population-based register has been used to monitor the incidence of cancer in Sweden over time[73]. This information is used not only for improving care but also for research at both national and international levels. Reporting all diagnosed cancer cases to the register is mandatory resulting in a high degree of completeness, but with some dependence on cancer types and patient age[74]. Quality controls ensure that submitted data are as correct as possible[75] and official reports are published each year in order to maintain quality of care.

3.1.2 The Swedish National Colorectal Cancer Register

The Swedish Rectal Cancer Register was established in 1995 while the Swedish Colon Cancer Register was founded first in 2007. The Northern Regional Cancer Centre is responsible for this register[76].

Data are collected prospectively and include patient-specific data (*e.g.* personal identification number, age, gender), cancer-specific data (*e.g.* pretherapeutic assessment and investigation, tumour site, tumour stage, date, type and duration of surgery, intraoperative blood loss, ASA score, complications, need and cause for intervise care unit (ICU) admission and reoperation, neo- and adjuvant treatment, 30-daypostoperative death, date and destination of discharge, and follow- up data (*e.g.* date and cause of death). Postoperative non–surgical complications are cardiovascular, infectious and neurologic events. Surgical complications include wound rupture, anastomotic leakage, ostomy complications, bleeding and indwelling catheter at discharge. Severity is classified according to the Clavien-Dindo system[77] (Table 2).

Clavien-Dindo-Classification	
Class	Consequences
1	No pharmacological treatment or surgical, endoscopic, and radiological interventions
2	Pharmacological treatment including blood transfusion or parenteral nutrition
3	Surgical, endoscopic or radiological treatment without (3a) and with general anaesthesia (3b)
4	Life-threatening, intensive care
5	Death

***Table 2**. Severity of postoperative complications according to Clavien-Dindo-system[77]*

3.1.3. The Swedish Prescribed Drug Register

Held by the Board, this automatically created and monthly updated register provides various data on prescribed drugs that are dispended in pharmacies throughout the country. These data are also coupled to the personal identification number of the patient[78].

This register is also used in statistics and research, improving our knowledge of drug use in order to improve health-care.

3.2 STUDY POPULATIONS/PATIENTS AND DATA COLLECTION

3.2.1 Study I

Data were retrieved from the SCRCR for all colon cancer patients (n= 15 255), and comparative characteristics were evaluated in the groups younger or older than 75 years. For further analysis, only patients undergoing resection were included (Figure 3).

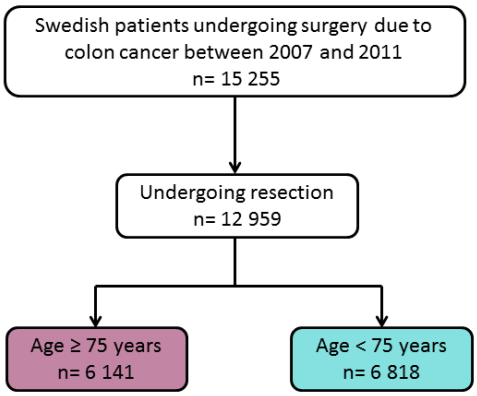

***Figure 3**. Flow chart of patients included in study I*

The age of 75 years was chosen to categorise groups for several reasons: it is close to the median age of patients with colon cancer in Sweden; it has been used in other studies[79,80], and a biological age of 75 years often serves as a breakpoint for oncologic treatment. Sex, tumour location, staging and MDT conference evaluation were analysed, surgical procedure, and whether or not it was performed as an emergency (defined as surgery for an acute medical reason within 2–3 days after admission to hospital).

Three main outcomes were compared:

- complete preoperative staging (imaging results available of local growth of the primary tumour and of liver and lung metastases)
- MDT conference evaluation
- curative resection (considered radical by the operating surgeon and deemed complete by the pathologist)

3.2.2 Study II

Data were retrieved from SCRCR and combined with the Swedish Prescribed Drug Register on 9 706 patients who underwent surgery due to CRC between 2007 and 2010 (Figure 4).

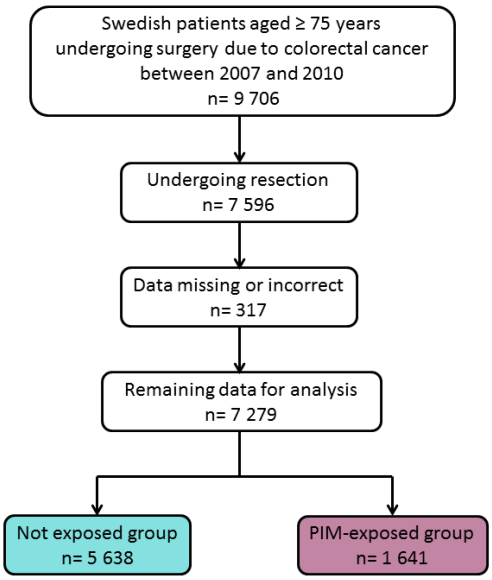

Figure 4. *Chart of included patients in study II*

Pharmaceutical data were obtained from the Swedish Prescribed Drug Register: date and number of dispensed receipts, the Anatomical Therapeutic Chemical (ATC) Classification code, defined daily dose and number of tablets per package. Drugs were included regardless of whether or not the prescription was for regular use or as required. Entries belonging to ATC groups V, X and Y (various, unidentified) were excluded.

From these data, the amount of available medication was calculated. If it covered at least 7 days before surgery and included the day of surgery, it was considered to be present.
Patients were then divided into two groups according to presence or absence of dispensed PIM in the Prescribed Drug Register. For the classification of PIM, we used three of the drug-specific indicators as classified by the Board[62] (Table 3):

- Drugs that should be avoided if no particular indication exists.
- Drugs for which a correct and current indication is of particular importance (not all drugs in this group were included).
- Polypharmacy (not all drugs in this group were included).

Medication	ATC code	Side-effects/risk for
PIM that should be avoided if no particular indication exists		
Long-acting benzodiazepines	N05BA01, N05CD02, N05CD03	Hang over, cognitive impairment, muscle weakness, balance problems, fall
Propiomazine	N05CM06	Hang-over, extrapyramidal symptoms
Tramadol	N02AX02	Nausea, cognitive impairment
Anticholinergics		Dry mouth, dry eyes, constipation, urinary retention, tachycardia, cognitive impairment
Urinary antispasmodics	G04BD	
Anxiolytics	N05BB01	
Antidepressants	N06AA	
Antihistamines for systematic use (1st generation)	R06AD	
PIM for which a correct and current indication is of particular importance		
Anti-inflammatory and anti-rheumatic drugs, non-steroids	M01A (excl M01AX05)	Gastrointestinal ulcer and bleeding, heart failure, fluid retention, renal decline, drug-drug interactions, cardiovascular events
Opioids	N02A (excl N02AX02, N02AG)	Cognitive impairment, fall
Psycholeptics	N05A (excl N05AN, N05AA)	Cognitive impairment, sedation, extrapyramidal symptoms, orthostatic hypotension
Antidepressants	N06AB, N06AX	Psychiatric and cognitive impairment, serotonergic syndrome
Digoxin	C01AA05	Drug interactions, arrhythmia, cognitive impairment, gastrointestinal side effects
Polypharmacy		
Combination of 3 or more Psycholeptics	N05A, N05B, N05C, N06A	Drug interactions, psychiatric and cognitive impairment, weakness

***Table 3**. Potentially inappropriate medication (PIM), used in study II, that should be avoided in drug therapy of elderly patients as classfied by the Board, their ATC code and side-effects[62].*

Two main outcomes were investigated regarding presence or absence of PIM at time of surgery:

- Length of stay in hospital
- 30-day-postoperative mortality

Independent variables, which were suspected to influence the outcome of surgery, were included in the multivariate analyses. These were: sex, age, ASA-classification, T-stage, clinical stage, type of surgical procedures, emergency or elective surgery, and postoperative surgical complication.

3.2.3 Study III

Participants were purposefully selected persons aged 75 years and above, who had recently undergone elective colorectal cancer surgery with curative intent between 2013 and 2014 at the Karolinska University Hospital, Stockholm, Sweden. Participants were required to read, speak and understand the Swedish language. Persons were excluded if long-term postoperative delirium was recorded during hospital stay or if there was a diagnosis of dementia.

The persons were sent a letter approximately 2 weeks after discharge requesting their participation. After this first contact, the persons were contacted by phone to ask whether or not they were positive to participation. If the person agreed, a location for the interview was decided upon that would promote the participant's feeling of comfort and security; at home if so wished. The individual face-to-face interviews were set three to eight months after surgery. Two participants wished to be interviewed at the surgical out-patient clinic. The interviews, lasting 45 to 90 minutes, were carried out by the last author using a semi-structured interview guide. The interviews were recorded on tape and data were transcribed *verbatim* (*i.e.* literally).

Interviews were used to explore the patient's experiences of:

- The healthcare process including primary investigation and diagnosis period, stay in hospital and rehabilitation centre, and recovery at home.
- Information given during the pre-, peri-, and postoperative period.

The interview guide was semi-structured and addressed the three time periods: preoperative, perioperative and after discharge (Appendix). Open questions were used to avoid bias, and clarifying questions were asked whenever necessary. The interview guide was tested on the first two participants and was found not to need adaption; thus these two interviews were included in the analyses.

Since we were interested in describing the experiences of the participants, inductive qualitative content analysis[81] was chosen. The aim of this qualitative approach is to analyse manifest (meaning) and latent (meaning between the lines) content of a text with focus on the subject and context. Similarities and differences in participants' experiences form patterns which can be interpreted.

Interviews were read and re-read by the first author. Meaning units were identified and in a second step condensed, *i.e.* the meaning unit is shortened while keeping its essence, and thereafter coded for their essential content. Subcategories were formed which then were gathered into categories. The abstraction process began after categorisation. The final step was to find a theme that united associated categories (Figure 5). Condensation, coding and sub- and categorisation were performed by the first author with continuous feedback with the last author. Theme abstract was conducted by the authors together so as to enhance validity.

Figure 5. *Analysis process with example of a quotation from patient no 7.*

3.2.4 Study IV

This prospective cohort study was performed at the Karolinska University Hospital between January 2010 and October 2016. Inclusion criteria were age 75 years or older at surgery, planned for elective surgery with curative intent for suspected CRC, with no preoperative oncological treatment. Exclusion criteria were surgery for other cancer, recent surgery for CRC, difficulties in understanding Swedish, and dementia.

Based on clinical experience with this group of patients, a sample size of 50 patients was chosen so as to include a broad spectrum of associated diseases, functional restrictions and social situations.

Patients were included from two surgical departments under Karolinska University Hospital (Huddinge and Solna Hospitals). Between 2010 and 2014, patients were included at the Huddinge department that mainly performed colon cancer resection. In 2014, reorganisation of the surgical clinic lead to the concentration of all CRC-surgery to the Solna department and thereafter inclusion comprised both colon and rectal surgery.

Potential participants were approached by a contact nurse or the surgeon at their first visit and asked if they were interested in participation. If they agreed, the geriatrician was informed and the patient contacted for further details and a suggested date, in proximity to the visit to the surgeon, for a comprehensive geriatric assessment (CGA). Patients were informed that results of the preoperative assessment could lead to postponement of surgery if the geriatrician recommended further action due to discovery of a geriatric problem. After accepting participation, a signed consent was obtained prior to or during the preoperative geriatric visit. The timing of assessment was between one day and three weeks prior to surgery.

Besides the preoperative geriatric assessment, follow-ups were planned at 1, 3 and 12 months after surgery, and screening for delirium was planned on postoperative Days 1 and 3 (Figure 6).

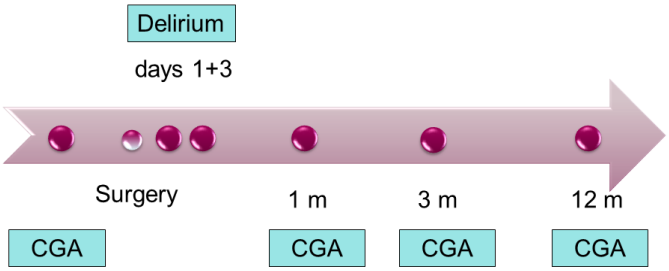

***Figure 6**. Algorithm of the study design. CGA – comprehensive geriatric assessment; m – month(s)*

The comprehensive geriatric assessment included:

- Health status: physical examination
- Social status
- Health-related quality of life: Eq-5D
- Functional status: Activities of Daily Living (ADL)
- Pressure ulcer risk: Modified Norton scale
- Nutrition: Mini-Nutritional Assessment (MNA-SF)
- Fall risk: Downton Fall Risk Index (DFRI)
- Cognition: Mini-Mental State Examination (MMSE)
- Mood: Geriatric Depression Scale 20 (GDS-20)

- Delirium: Confusion Assessment Method (CAM)

In addition, the participants were assessed regarding comorbidity using the Charlson age-adjusted comorbidity index (ACCI). Physical fitness was assessed by an anaesthesiologist who decided the ASA grade, and a review of medication was carried out. Retrospective assessment using the triage risk screening tool (TRST) was performed to assess if a patient could be at risk for functional decline.

3.2.4.1 Description of assessment instruments

The tools used in the CGA were chosen on the basis of frequent use in day-to-day healthcare at the participating hospitals. The CGAs were conducted by one of five geriatricians aquainted with the study methodology.

EuroQol-5-Dimensions

This standardised self-rating scale for health- realted quality of life (HRQoL) is used in quality follow-ups in health care and clinical research and was developed by the EuroQol-group[82]. It contains five items (mobility, hygiene, activities, pain/discomfort and anxiety/depression) and can be graded in three levels of severity:

- 1 – no problems
- 2 – some problems
- 3 – major problems

The grading is translated into a health-index using mathematical calculations, and a value of 1.00 equals full health whilst an index of 0.00 equals death[83]. Even negative results (minimum -0.594) are possible, *i.e.* conditions rated worse than death. HRQoL has been produced specifically for different countries; in Sweden, HRQoL has been described in a general Swedish population[84] and is used as basis for health-index calculations in Sweden.

Activities of daily living (ADL)

Developed as a practical tool for the assessment of the functional abilities of disabled persons[85], the ranking of these daily self-care activities correspond to the development of abilities from childhood and, in reverse, the loss of these abilities with age or disease. Also named basic ADL, the Katz ADL index describes the independency/dependency according to the following degrees:

- A – independence in all six activities
- B – Dependence in one activity
- C – Dependence in bathing and one additional activity
- D – Dependence in bathing, dressing and one additional activity

- E – Dependence in bathing, dressing, going to the toilet and one additional activity
- F – Dependence in bathing, dressing, going to the toilet, transferring and one additional activity
- G – Dependence in all activities

Modified Norton Scale

The Norton scale[86] is used in day-to-day healthcare to assess the risk for pressure ulcers. It assesses the physical and mental condition, food and liquid intake, mobility, and continence. Scores range from 7 to 28 and risk for pressure ulcer is indicated by a score of 20 points or lower.

Mini Nutritional Assessment – Short Form

In 1994, the Mini Nutritional Assessment was developed and validated for nutritional screening in elderly persons[87]. In 2001, a short form (MNA-SF) was developed and validated[88] and is widely used in healthcare. The MNA-SF comprises five variables: body mass index, weight loss, low food intake, acute disease or physical stress over the past three months, mobility, and cognitive impairment. The score ranges from 0 – 14. A score of 11 points or lower indicates risk for malnutrition and that further assessment and intervention is recommended.

Downton Fall Risk Index

Fall risk is assessed using the DFRI[89], even this tool is widely used at our hospital. Addressed items are previous falls, medication with high risk for causing falls (tranquilisers, sedatives, diuretics, antihypertensives, antiparkinson drugs, and antidepressants), visual and hearing impairment, limp, cognitive impairment, and unsafe gait. Scores range from 0 to 11, and a score of 3 or more indicates increased risk for fall.

Mini-Mental Status Examination

Cognition was tested using the MMSE test, widely used in healthcare as an initial screening for dementia. Scores range from 0 to 30 points, 24 points and lower indicate cognitive impairment[90] and further assessment is recommended if deemed relevant. The MMSE is dependent on the intellectual capacity of the test person[91] and must be individually interpreted but is a useful tool as a marker over-time[92].

Geriatric Depression Scale-20

The self-rating GDS-20 consists of 20 questions including sleeping habits, worries, pain, suicidal thoughts, mood, and activity habits in comparison to one year previously, and change

of habit is the essential result. A score of 6 or more indicates possible depression requiring further assessment[93].

Confusion Assessment Method

The Confusion Assessment Method (CAM)[94] is a commonly used tool for the detection of delirium in routine clinical care[95], and assesses nine items: acute onset and fluctuating course of confusion, inattention, disorganised thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbance, increased or reduced psychomotor activity, and disturbance of the sleep-wake cycle. The presence of both acute onset and fluctuating course of confusion and inattention, together with an observation of either disorganised thinking or altered level of consciousness is required for the diagnosis of delirium.

ASA score

A commonly used assessment of the physical status of patients prior to surgery is the American Society of Anesthesiologists (ASA) classification[96,97].

- ASA 1 – healthy patient
- ASA 2 – mild systemic disease
- ASA 3 – severe systemic disease
- ASA 4 – severe systemic disease which is a constant threat to life
- ASA 5 – moribund patient not expected to survive without surgery
- ASA 6 – a patient declared brain-dead patient whose organs are being removed for donor purposes

Age-adjusted Charlson Comorbidity Index

The Charlson Comorbidity Index has been developed to assess the surgical risk of elderly patients. A further development of this index was the version with age-adjustment[98].

Scoring system (one count for each condition)[99]:

- 1-4 point(s) – For each decade over 40 years, maximum 4 points
- 1 point – Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes (insulin treated)
- 2 points – Hemiplegia, moderate/severe renal disease, diabetes with end-organ damage, any tumour, leukaemia/lymphoma
- 3 points – Moderate/severe liver disease
- 6 points – Metastatic solid tumour, AIDS (acquired immune deficiency syndrome)

The ACCI predicts the 1-year mortality risk after surgery: A score of 0 is used as reference (1.00). The estimated relative risk of death one year after surgery increases with increasing score. A score of 5 (*e.g.* age 75 years and older and solid tumour) has an estimated relative risk of death of 6.38 (99% CI 3.07 - 13.2) and a score of 8, the estimated relative risk of death is 19.37, which is the maximum (99% CI 6.01 - 62.40)[98].

Triage Risk Screening Tool

The Triage Risk Screening Tool (TRST)[100] is a tool comprising 5 items with "yes/no" answers: cognitive decline, living alone/no care giver, walking difficulties, hospital admission during the previous three months, and 5 or more medication. The maximum score is 6 points, and the threshold for being a geriatric risk patient is 2 points.

Postoperative delirium

At postoperative days 1 and 3, a geriatrician assessed the participants regarding the presence of delirium (POD) using the CAM[94].

Follow-up

CGA was performed at the 1-, 3- and 12-month follow-up-visits. The 1-month visit was combined with the scheduled revisit to the surgeon, whilst the 3- and 12-month visits were to the geriatrician alone.

At the 1-month visit, assessment for depression was excluded due to the potential confounding effect of surgery *per se* on this parameter.

Comparative population

During the study period, suspicion was raised that the patients included did not represent an ordinary geriatric population; only relatively healthy patients, for instance, accepted participation. To assess the external validity, data from the SCRCR was extracted to allow comparison with elective CRC surgery patients living in Stockholm County but not operated at Karolinska University Hospital. The same inclusion criteria were used.

The main outcomes were:

- Postoperative complications (medical and surgical complications, including postoperative delirium revealed by screening and death within 30 days after surgery)
- Length of hospital stay
- Follow-up at 1, 3, and 12 months postoperatively

3.3 STATISTICAL ANALYSES

Quantitative statistical methods were used in studies I, II, and IV. Statistical analyses were performed using STATISTICA 10 (Statsoft, Tulsa, OK, USA) (Study I, II, and IV) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA) (study I). Mean, standard deviation, median, range and percentage were used for descriptive purposes. The two-tailed χ^2-test and Fishers exact-test were used for comparison of dichotomous data between groups. The Mann–Whitney-U-test was used for comparison of continuous and categorical data.

Uni- and multivariate logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals. The P-value limit, indicating statistical significance, was set at $p<0.05$. Patients with missing values were automatically excluded in the logistic regression for that specific independent variable, hence there are different numbers of patients in the different analyses.

In study I, age, sex and tumour location were all included in the multivariate analyses regardless of significance in the univariate analyses whilst other factors were only included in the multivariate analyses if significant in the univariate analyses. If not significant in the multivariate analyses, factors were stepwise excluded (the factor with the highest P-value first). For the main outcomes, analyses were also performed in smaller age cohorts.

In study II, LOS and age were dichotomised using the median for the entire group as cut-off-value for the logistic regression analysis. Variables assumed to influence surgical outcome were included in the multivariate analyses.

In study IV, assumed dependent variables were dichotomised according to either median in the baseline characteristics (Eq5d, ACCI) or the clinically relevant cut-off-levels (ADL, Norton, MNA-SF, MMSE, GDS-20, polypharmacy, TRST). For analyses of the CGA-follow-ups, paired T-test and Wilcoxon matched pairs test were used.

Study III is a qualitative study using inductive content analysis.

3.4 ETHICAL CONSIDERATION

The studies included in this thesis follow the declaration of Helsinki[101] and were approved by the Regional Ethics Committee in Stockholm:

- Study I & II: Karolinska Institutet Dnr 2011/938-31/1
- Study III: Karolinska Institutet Dnr 2009/1479-31/5
- Study IV: Karolinska Institutet Dnr 2009/2105-31/1; 2013/690-32; 2016/895-32/1

3.4.1.1 Studies I and II

The register-based studies in this thesis have no direct impact on the patients involved since they are analyses of already prospectively sampled data. It is widely acknowledged that register databases are an important cornerstone in quality assurance of healthcare, as well as being an important source of research information. Consent for research is given by acceptance of inclusion in these registers. In recent years this has become the target of criticism. The argument against register-based research mainly concerns the potential violation of the Swedish Data Privacy Act and use of data without consent of the patient. However, all studies, including register data studies, have to be approved by a regional ethics committee.

Data from two registers were matched in Study II, and after that blinded by the Swedish National Board of Health and Welfare, which means that we did not have access to information that could be traced back to specific patients in the study.

3.4.1.2 Study III

The participants signed a written informed consent before the interview and were informed about the voluntary nature of the study and confidentiality. Neither the first nor the last author took part in the care process which ensured neutrality in the relationship between interviewer and participant.

Due to the fact that the participants were former patients still recovering at the time of the interview, there was a risk of reviving painful and unpleasant memories from their time in hospital. In such cases, the interviewer recommended contacting the patient-responsible nurse at the surgical department or the general practitioner. On the other hand, participation in the study could have had a psychologically positive effect by allowing the participant to reflect and discuss possible unpleasant experiences related to their care at the surgical ward.

3.4.1.3 Study IV

In this study, data from the colorectal cancer register were matched with data from the same patient retrieved from the medical records. After the fusion of databases, the patients' personal identity numbers were deleted. All study visits were documented in the notes and handled with strict confidentiality. Patients who did not participate in the study were treated according to the standard care programme.

Ethical approval for survey of the medical records of patients operated for CRC but not included in the study was received later (2013/690-32), as well as an amendment enabling inclusion of the two patients who had not turned 75 years at surgery (2016/895-32/1).

4 RESULTS

4.1 STUDY I

Patient Characteristics

Between 2007 and 2010, 15 255 patients were diagnosed with colon cancer in Sweden. Of these, 7 270 were patients 75 years and older. Basic characteristics are shown in Figure 7. Resection surgery was performed in 12 959 patients (6 141 were 75 years and older). Their basic characteristics are shown in Figure 8. Further analyses were limited to the resection-cohort.

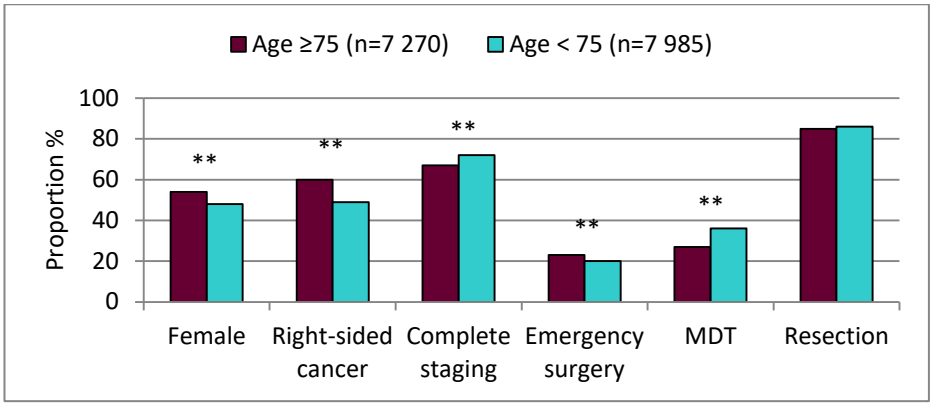

Figure 7. *Basic characteristics (%) of all patients diagnosed with colon cancer between 2007 and 2010 in Sweden. Significant differences between the age groups are indicated in the figure (**p < 0.001).*

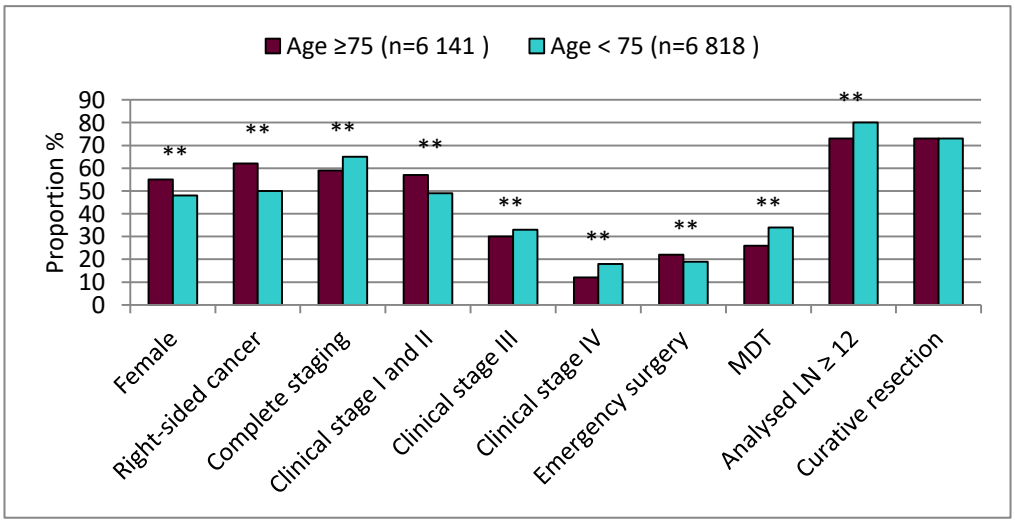

Figure 8. *Basic characteristics (%) of all patients who underwent resection due to colon cancer between 2007 and 2010 in Sweden. Significant differences between the age groups are indicated in the figure (** p < 0.001). LN – lymph nodes.*

Main outcomes

Incomplete staging

Patients requiring emergency surgery were excluded from the analysis.

Table 4 shows significant risk factors not to be staged completely prior to surgery. Sex, tumour location (left- or right-sided), T-stage and clinical stage were not associated with incomplete staging in the multivariate analysis.

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P
Age ≥ 75 years	1.26 (1.16-1.37)	1.16 (1.06-1.26)	0.002
No MDT conference	2.94 (2.67-3.24)	2.72 (2.46-3.01)	< 0.001

Table 4. *Univariate and multivariate logistic regression analyses of factors associated with incomplete staging prior to surgery in patients undergoing elective resection for colon cancer.*

No MDT conference-evaluation

In this analysis, patients with emergency procedures were also excluded since there was by definition no time for a MDT conference. Higher age, right-sided tumour location and incomplete staging were risk factors for not being discussed at a MDT conference (Table 5) whilst sex showed no association in the multivariate analyses. Patients with T-stage 4 and clinical stage IV are more frequently presented at a MDT conference.

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P
Age ≥ 75 years	1.42 (1.31-1.55)	1.33 (1.22-1.45)	< 0.001
Right-sided tumour	1.23 (1.13-1.33)	1.17 (1.07-1.28)	< 0.001
Incomplete staging	2.94 (2.67–3.24)	2.71 (2.45–3.00)	< 0.001

Table *5. Univariate and multivariate logistic regression analyses of factors associated with no MDT evaluation prior to surgery in patients undergoing elective resection for colon cancer.*

Non-curative resection

In the analysis of "non-curative resection" clinical stage IV patients were excluded (≥75 years n= 677; ≤75 years n= 1134). Table 6 shows risk factors for non-curative resection. Sex was not associated with non-curative resection in the multivariate analyses.

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P
Age ≥ 75 years	1.20 (1.08-1.34)	1.19 (1.06-1.33)	0.004
Right-sided tumour	1.15 (1.03-1.29)	1.18 (1.04-1.32)	0.007
T-stage 4	4.21 (3.72–4.76)	3.37 (2.96–3.84)	< 0.001
pTNM III	2.21 (1.98–2.47)	1.84 (1.64–2.07)	< 0.001
Emergency procedure	3.18 (2.81–3.59)	2.59 (2.27–2.95)	< 0.001

***Table 6**. Univariate and multivariate regression analyses for factors associated with non-curative resection in patients undergoing elective resection for colon cancer.*

Outcomes affected by age: "complete staging", "MDT conference" and "curative resection"

When stratifying patients undergoing resection surgery according to age, there was a significant age-dependent difference (p<0.001) in complete staging, MDT conference and curative resection (Figure 9).

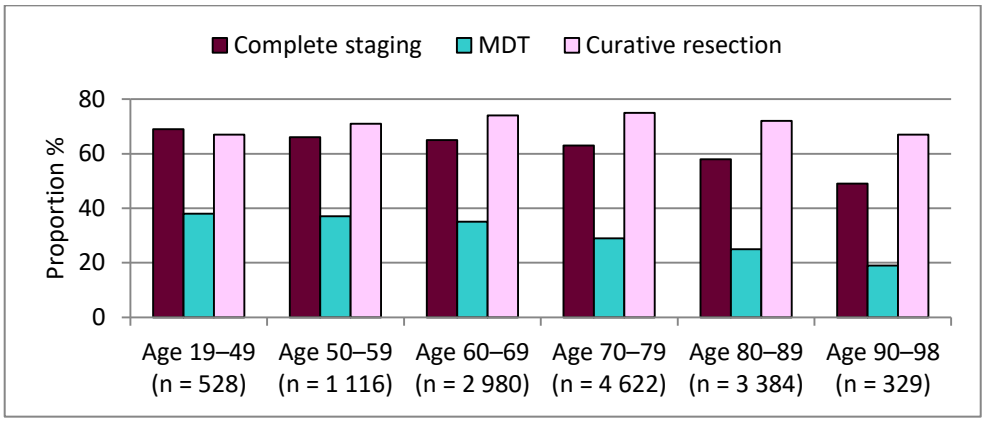

***Figure 9.** Proportion of patients completely staged, discussed at MDT conferences before surgery and undergoing curative resection divided into age cohorts. (P<0.001).*

Emergency surgery

Of the 12 959 patients undergoing resection surgery, 20.2% were performed as an emergency procedure (n= 2 612). Patients ≥75 years underwent emergency surgery more frequently than younger patients (n=1 330; 23% vs. n= 1 282; 20%, p<0.001). Obstruction and perforation as indications for emergency surgery were similar in both groups (75% vs. 78% respectively 14% vs. 15%) whilst bleeding was more often the reason for emergency surgery in the older group (7% vs. 2%, p<0.001). Cancer stage was less advanced in this older population.

4.2 STUDY II

Patient Characteristics

In total 7 279 elderly patients (age ≥ 75 years) undergoing surgical resection due to colorectal cancer 2007-2010 in Sweden were included in this study; 22.5 % had at least one PIM. The median number of total drug prescriptions (PIM-group vs. non-PIM-group) was 6 and 3 drugs respectively (p <0.001). The mean age in both groups was similar (81.8 vs. 81.2 years; p <0.001). Further patient characteristics are presented in Figure 10.

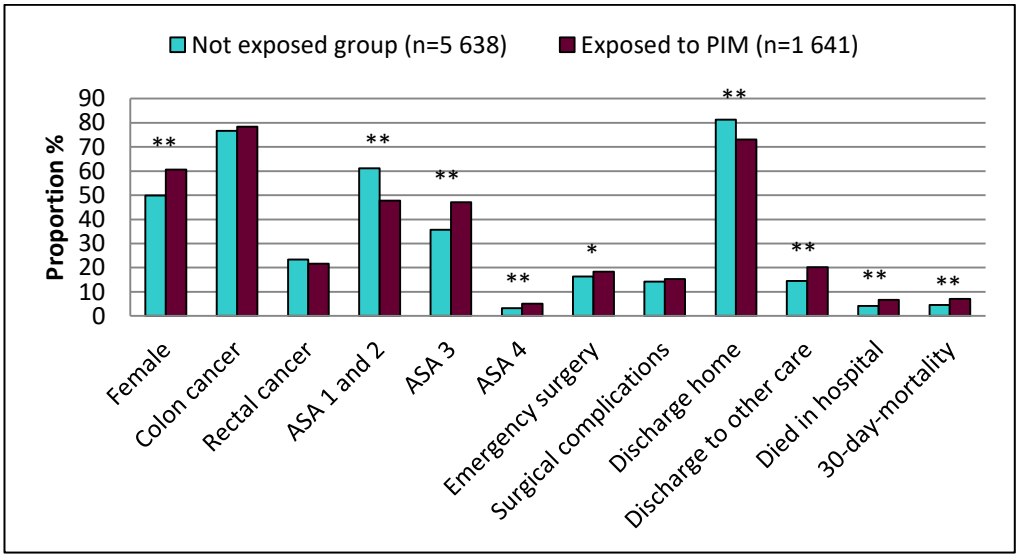

Figure 10. *7 279 patients undergoing surgical resection due to colorectal cancer 2007-2010. Comparisons are made between the patients defined as users of PIM at least one week prior to surgery and patients not exposed to PIM (*p<0.05;** p < 0.001).*

Potentially inappropriate medication

In total, 1 641 patients had been prescribed at least one PIM at the time of surgery; some patients had multiple PIM. Proportions of PIM are displayed in Figure 11.

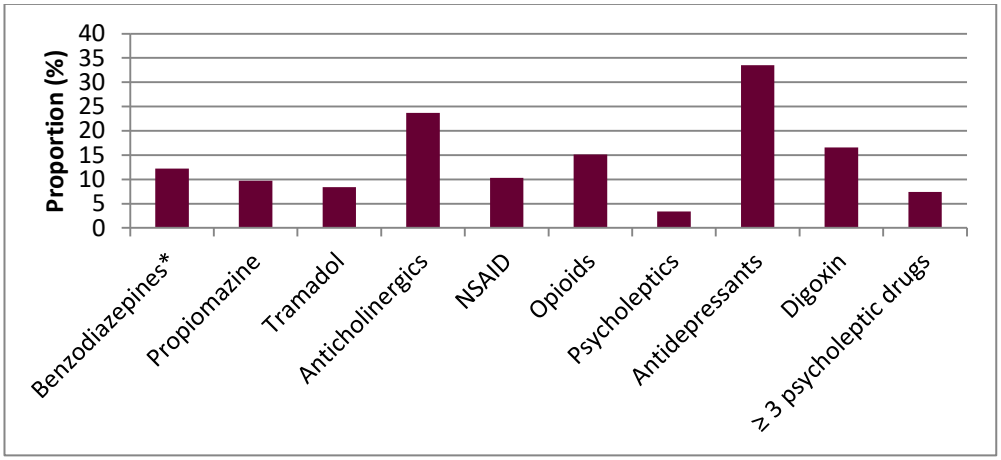

Figure 11. *Proportion of potentially inappropriate medication according to the Board[62] in 1 641 elderly patients undergoing CRC surgery. Patients can have several PIM. (*-long-acting)*

Main outcomes

The median LOS in the non-PIM group was 9 days compared to 10 days in the PIM group which was still significant when controlled for independent factors in the multivariate analyses (OR 1.14, 95% CI 1.00–1.29; P = 0.046).

Death within 30 days after surgery was 7.1% in the PIM group compared to 4.5% in the non-PIM group, and this difference remained significant after adjusting for independent variables in the multivariate analyses (OR 1.43, 95% CI 1.11–1.85; p = 0.006).

4.3 STUDY III

The last author in this study approached 19 patients at the Karolinska University Hospital surgical department. Of these, 16 patients accepted participation; eight men (aged 76-89 years) and eight women (77-84 years). All participants were living in their own accommodation, six were married or in a relationship, ten were widowed. All participants were living in the Stockholm County and had different socio-economic backgrounds.

Interviews reached saturation after 12 patients, *i.e.* no new information could be obtained for the purposes of the study. After discussion, four more patients were included to assure that no additional information had been missed.

The healthcare process was divided into three time periods:

- *The preoperative period:* from symptom start or the occurrence of abnormal clinical signs and primary care investigation, to subsequent investigation and management planning by the surgical clinic.
- *The perioperative period:* from the day of admission prior to surgery until the day of discharge home or to a rehabilitation facility.
- *The postoperative period:* from the time of discharge from the surgical ward until the actual interviews were conducted (included time in rehabilitation facility and recovery at home).

After extraction of citations from the interview analyses, themes were created describing how the participants experienced the healthcare process and the information given by the healthcare professionals (Tables 7 and 8). To illustrate these experiences, quotes are stated to underline the themes (Figures 12 and 13).

How participants experienced the health care process

In general, experiences of the surgical care process varied greatly but several themes occurred repeatedly. During the preoperative period, unfamiliar symptoms caused many participants to feel alone, worrying about the cause and fearing the impact on their future life. Several participants had to struggle to be heard by their general practitioner when they suspected that something was wrong, generating feelings of exposure, vulnerability and loss of control. Relief, but also shock and grief were feelings when the cause (*i.e.* cancer) was discovered. Similar feelings were expressed during the perioperative time; dependency on care providers and worries about surgery and how life will become afterwards were evident. After discharge there were questions and considerations to be addressed, and one of the prominent experiences was a feeling of being abandoned by primary and specialist care. Rehabilitation was not experienced as being tailored, causing disappointment in several participants. Struggling with recovery (*e.g.* wound care or nutritional difficulties) was regularly described as a problem, but in most cases this was not taken seriously by healthcare professionals, leaving the participants with feelings of uncertainty and anxiety.

Preoperative (time until admission)	Perioperative (admission-discharge)	Postoperative (time after discharge)
Feeling alone	Feeling exposed	Feeling disappointed
Feeling relief	Feeling vulnerable	Feeling abandoned
Feeling vulnerable	Existential feelings	Feeling anxious
Experience of shock and grief	Seeking peer support	Feeling uncertain
Philosophical thoughts		
Feeling discriminated		
Feeling out of control		

Table*7. Themes for experiences felt of the healthcare process*

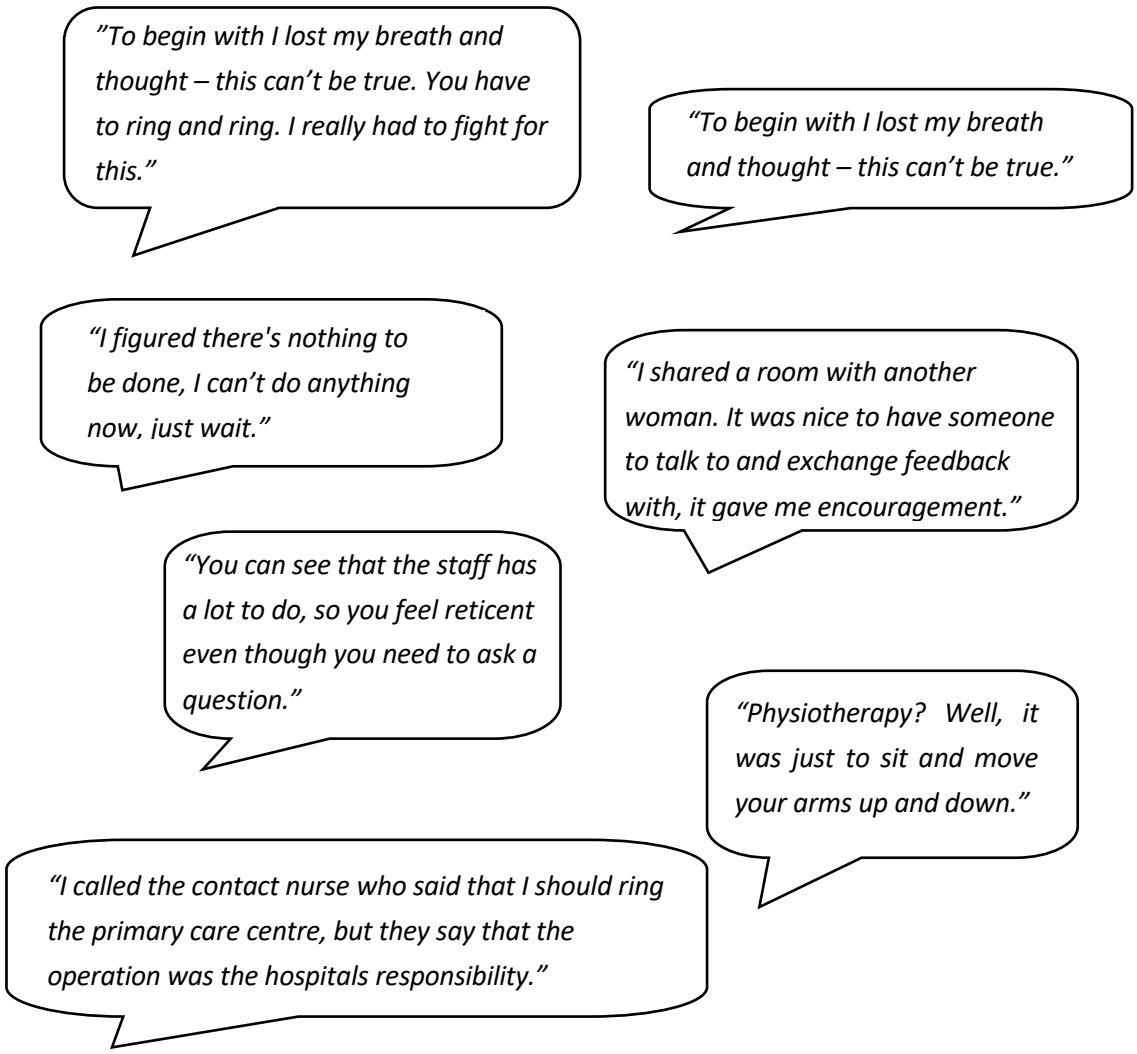

Figure 12. *Examples of patients' quotes regarding experiences of the health care process.*

Experiences of information provided

The information provided by the healthcare providers was perceived differently. A few patients had no problems and were satisfied with the information received, but most participants experienced difficulties in understanding. Several participants mentioned the use of inappropriate incomprehensible medical language. The point in time when information was given was also important; several participants described that they had difficulties in concentrating on any information after receiving the diagnosis of cancer. Considerations and questions often emerged afterwards, leaving participants wondering whom to address with their concerns. In particular during the preoperative period, many experienced lack of information regarding stoma care, change in body functions and the treatment planned. Lack of time for reflection and additional information was experienced during the perioperative period, when participants experienced staff to be too occupied to take heed, and the hospital environment as being strange and bothering. After discharge,

there was little information on how to move on, what to expect and whom to address questions when needed.

Preoperative (time until admission)	Perioperative (admission-discharge)	Postoperative (time after discharge)
Not susceptible	Feeling vulnerable	Feeling uncertain
Fearing the prospect of a stoma	Strange environment	Lack of information
Fearing bodily changes		Difficult to understand information
Acceptance/adapting to bodily changes		Feeing disappointed

***Table** 8. Themes for the experience of information provided during the healthcare process*

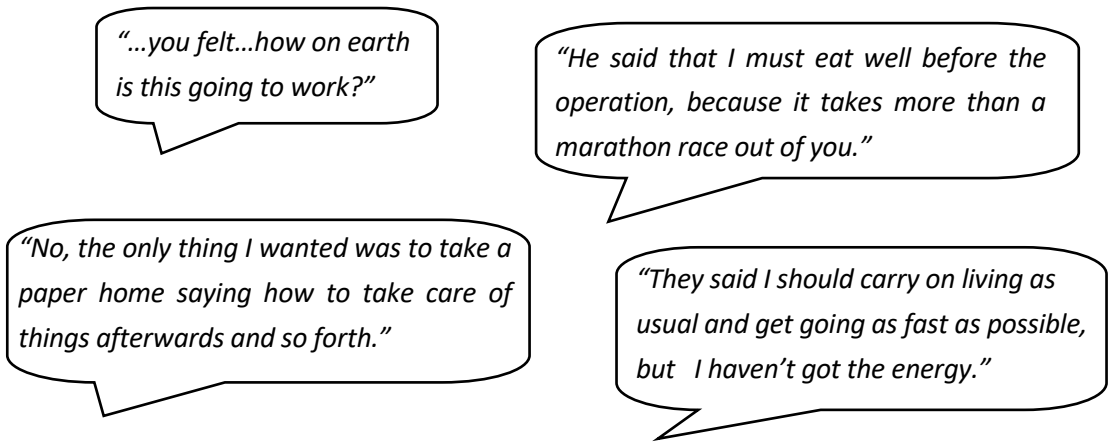

***Figure 13.** Examples of patients' quotes regarding information provided.*

4.4 STUDY IV

Patient Characteristics

In this study, 50 patients underwent a complete geriatric assessment (CGA) prior to surgery for suspected colorectal cancer. During the enrolment period between January 2010 and November 2016, a total of 62 patients accepted participation, 50 of these underwent geriatric assessment. For one patient, treatment plans were changed due to decline in health status so that this patient did not undergo surgery, leaving 49 patients entering the study protocol. 39 patients reached complete follow-up (Figure 14).

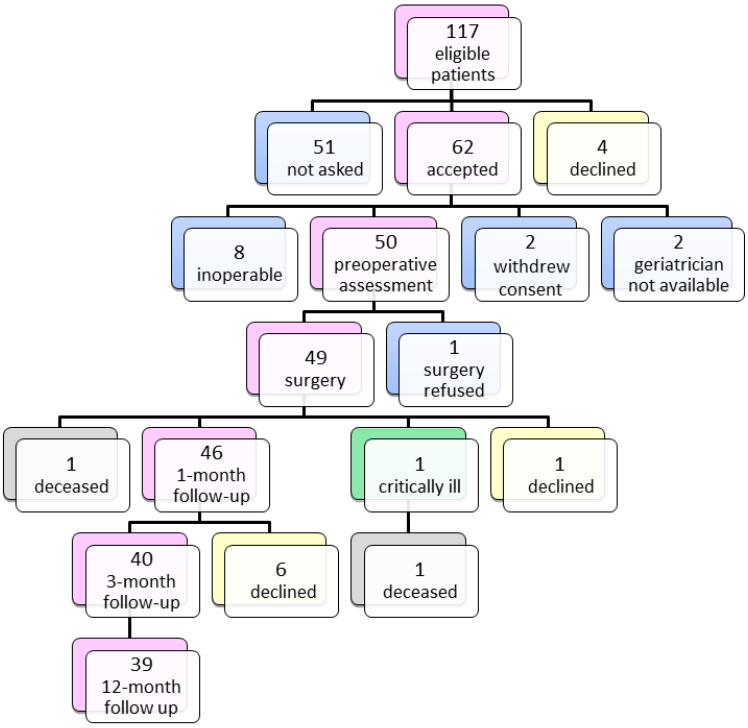

Figure 14. *Flow chart of patients inclusion and follow-up of study IV.*

The mean age of the study patients was 81 years (range 74-89). Twenty-six were women and in 44 patients, the tumour was located in the colon. Malignancy was confirmed by pathology in 45 out of 49 cases but all were included since the surgical procedure remained the same. Stage II tumour and ASA class 3 were the most common. Three patients required intensive care and four underwent reoperation. Thirty-three patients were discharged to other wards, including rehabilitation facilities, whilst 14 were discharged home.

The perioperative characteristics of the study cohort were retrieved from the SCRCR and compared with those of a group of Stockholm County patients undergoing elective CRC surgery in other hospitals than Karolinska University Hospital (n=1 137). Postoperative complications were fewer in the study group (24.5% vs. 32.4%; $p<0.001$) but Clavien-Dindo class distribution did not differ. LOS was similar in both groups, but fewer patients in the study group were discharged home but instead transferred to other care facilities. The 30-day postoperative mortality rates were similar.

Comprehensive geriatric assessment

The CGA of the 49 patients who underwent surgery are shown in Table 9. When assessed for geriatric risk profile (TRST), 32 patients had scores 2 or higher (65%).

Assessment	Tool		
Health-related quality of Life	EQ-5D	Range Mean (SD)	-0.016-0.919 0.765 (0.178)
Activities of Daily Living	Katz-ADL	Independency (A) (n) Moderate dependence (B-D) (n) Dependence (E-G)	43 6 -
Pressure ulcer risk	Modified Norton	Patients at risk for pressure ulcer (n) Range Mean (SD)	2 16-28 25.8 (2.3)
Nutrition Status	MNA-SF	Patients at risk for malnutrition (n) Range Mean (SD)	19 6-14 11.5 (2.3)
Fall risk	DFRI	Patients at risk for fall (n) Range Mean (SD)	22 0-6 2.4 (1.6)
Cognition	MMSE	Patients with cognitive impairment (n) Range Mean (SD)	4 23-30 27.4 (2.0)
Depression	GDS-20	Patients at risk for depression (n) Range Mean (SD)	13 0-16 4.0 (3.8)

Table 9. *Description of the preoperative comprehensive geriatric assessment in 49 eldery patients in study IV.*

No surgery was postponed as a result of the preoperative geriatric assessment. For 7 patients, the geriatrician asked for further contact with a dietician (14%). Primary care was contacted for further assessment of depression (n=1), cognitive impairment (n=1), osteoporosis (n=2), and change in diabetes medication due to decline in renal function (n=1). In one case, the geriatrician recommended stopping intake of Omega-3 prior to surgery. One patient presented with mild hyperkalaemia which was controlled and later shown to be normal.

Main Outcomes

Postoperative complications

Overall, postoperative complications occurred in 16 patients: anastomotic leakage (n=4), septicaemia (n=2), high stomal output, postoperative intestinal dysfunction, postoperative bleeding, pulmonary embolism, and oesophagitis (n=1 for each). According to the SCRCR, postoperative delirium was reported in one patient. The geriatric assessment revealed a total

of eight POD patients (7 patients as well as the patient in which POD was actually registered). Three of the positive screened patients had concomitant postoperative complications.

Due to logistical reasons such as holiday periods or short or no notice of changed operation date, 11 patients were not assessed for delirium at all. In these cases, the medical records were reviewed regarding information on sleeping, cognitive or psychiatric disturbance. In this way, one additional participant with postoperative delirium was identified.

One patient died within 30 days after surgery, another patient died within 60 days postoperatively.

None of the variables in the CGA showed a significant association with the occurrence of a postoperative complication. There was a slightly lower risk associated with malnutrition in the univariate analysis (OR 0.25; 95% CI 0.05-1.23; p=0.09) whilst risk for fall was associated with a slightly higher rate (OR 2.92; 95% CI 0.85-10.04; p=0.09).

Length of stay in hospital

The median length of stay was 8 days (range 5-43 days). None of the variables in the CGA showed a significant association with the LOS. Risk for malnutrition was associated with a slightly shorter LOS (OR 0.33; 95% CI 0.10-1.10; p=0.07) in the univariate analysis.

Follow-up

Most variables assessed remained at baseline levels. One exception was the health-related quality of life which fell significantly during the year following surgery. The nutritional status decreased significantly at the 1 month follow-up but had improved by the 3 and 12 month follow-up above baseline. Fall risk decreased at the 1-month follow-up but showed baseline levels at the 3 and 12 month follow-up.

5 DISCUSSION

Although CRC is a disease of elderly patients, management, treatment and care is not adapted to the special needs of this patient group. The overall goal of this thesis was to critically assess and analyse the surgical care of elderly CRC patients from various points of view hoping to identify necessary interventions and potential improvements. This included management and treatment of patients with colon cancer, the impact of PIM on CRC surgery outcome as well as the experiences felt by elderly CRC patients regarding the surgical care process and the information provided. Finally, the potential of a comprehensive geriatric assessment as a tool for the prediction of postoperative outcome and recovery of elderly patients after CRC surgery was investigated.

This thesis highlights the importance of adapting information and preoperative interventions (*e.g.* removal/adjustment of inappropriate medications) to the needs of the elderly CRC population, although the exact preoperative interventions that are effective in this respect remain to be determined. It is of paramount importance to offer both elderly and younger patients optimised and individualised preoperative staging and evaluation, and radical surgery whenever possible. Although more research into this subject is required, the results of this thesis confirm that there is a need for improvement in the management of colorectal cancer in elderly patients.

5.1 PREOPERATIVE CONSIDERATIONS

5.1.1 Management

Routine management of elderly colon cancer patients differs from that of younger patients as shown in study I. Women are overrepresented and tumour stages are often earlier which is in accordance with findings in other studies[79]. Complete staging (*i.e.* investigation of local tumour growth and distant metastases) was less often performed. Elderly patients were also underrepresented at multidisciplinary team conferences, the discussion forum of surgeons and oncologists when deciding on which treatment is most suitable for each patient. The importance of this forum in leading to an increase in the use of chemotherapy and improved survival has been stressed previously[10].

Current Swedish guidelines emphasise that all patients with colorectal cancer should be assessed for local tumour growth and distant metastases, and their case subsequently discussed at a MDT conference. Despite this, study I showed that elderly patients (>75 years) were less often discussed at a MDT conference than their younger counterparts (26% vs. 36%) and this was associated with less detailed tumour staging. After 2010, a substantial

increase in the number of cases discussed at MDT conferences prior to CRC surgery occurred[76]. MDT conferences provide an excellent opportunity to extend our expertise by involving a consultant with geriatric specialisation, addressing specific issues associated with elderly CRC patients, as highlighted for example by the SIOG[53]. These considerations led to the initiation of study IV where CRC patients planned for elective surgery underwent a comprehensive geriatric assessment.

5.1.2 Comprehensive geriatric assessment

The use of a comprehensive geriatrics assessment has been tested in many studies in various specialities, and there is a variety of tools that may be used in the CGA. In this thesis, the assessment instruments used in study IV were well-established and used in everyday practice at our hospital. We were unable to show an association between any specific preoperative geriatric assessment variable and outcome (postoperative complication and length of stay). This could possibly indicate that most elderly patients undergoing surgery for colorectal cancer cope with the strain of surgery better than expected. It is also possible that the assessment tools used might not have been sensitive enough for patients who are multimorbid by definition but otherwise have a good functional status. An additional factor that could affect LOS is that within Stockholm's healthcare organisation, geriatric patients are often transferred to geriatric or medical wards after surgery in order to provide further care. The results from the SIOG study[60] shows that there is an awareness of the usefulness of geriatric assessment and optimisation prior to surgery, but surgeons are still dubious because of the divergent results of the various tools and interventions.

Since CGA is time- and resource-consuming, it could be useful to first screen for potential candidates prior to surgery, and by doing so, identify frail patients at risk for geriatric events or impaired outcome. These individuals could then be subjected to further evaluation, including CGA. This screening assessment (TRST) was done retrospectively as a complement during analyses in study IV, using information retrieved from the patients' medical and study records. Although we could not show any association between TRST results and postoperative complications or LOS, it would be interesting to design a prospective and randomised study testing the impact of TRST screening, with subsequent CGA results available at the time of the MDT evaluation, on postoperative outcome and LOS.

5.1.3 Medication use

The presence of multiple medications is one consequence of aging and its associated morbidity. As regards surgery, medication can alter physiological responses and influence

anaesthesia, pain management and further necessary pharmaceutical treatment. In study IV, polypharmacy (defined as 5 or more medications prescribed daily) was present in 67% of the study patients.

Results from study II showed an association between the presence/intake of at least one PIM at the time of surgery and higher LOS and 30-day postoperative mortality. PIM have previously been shown to be associated with an increased risk for geriatric events such as delirium[102,103] and falls[104] which are also considered postoperative complications leading to prolonged length of hospital stay[105,106]. The register used in study II did not contain any information about the diagnoses leading to prescription of PIM, and hence the dataset may well include well-motivated prescriptions as well as outdated and/or inappropriate prescriptions. One example is digoxin for frequency control in cardiac dysrhythmia. This may be prescribed in elderly patients despite the caution necessary in persons with reduced renal function[107]. Other PIM, such as antidepressants, might be indicated in order to improve the patient's quality of life. Preoperative withdrawal, with its possible effects and impact on physiological status[108] must be balanced against the risk for worsened outcome after surgery with continuation of the drug.

In the United States and Europe, the prevalence of PIM in the elderly differs between elderly persons in the community (12%) and nursing home residents (40%)[109]. Nursing home residents tend to suffer from multimorbidity and geriatric syndromes, and as a consequence may not be suitable candidates for surgery. In study II, we gauged physical status on preoperative ASA-class assessment since the SCRCR did not provide data on comorbidity. In order to adjust for the confounding effect of comorbidity/decline in physical status on postoperative outcome, we included age and ASA-class in the multivariate analyses. These showed that the presence of PIM remained as an independent risk factor for prolonged LOS and increased postoperative mortality. The impact of general anaesthesia and sedation on postoperative delirium and cognitive dysfunction has been the focus of previous research without the finding of a convincing association[110], and few studies have investigated the impact of regular medication prior to surgery. In a recent study on 1 846 elective non-cardiac surgical patients, anxiolytics but not antidepressants were associated with increase in both 30-day postoperative mortality and major morbidity after adjustment for pre- and perioperative risk factors[111]. In study IV, we directly assessed physical status and saw that patients undergoing surgery had considerable comorbidity, and it may well be that a similar situation regarding comorbidity existed as for the patients investigated in study II.

In study II, we used information about prescribed medication and focused our attention on PIM. In Sweden, it is possible to purchase over-the-counter drugs (OTC), *i.e.* not requiring prescription, in pharmacies and stores. Data on such medication is therefore not available. Several of these OTC drugs, such as NSAIDs are potentially inappropriate in the elderly population. Patients might be unaware that the concurrent use of OTC drugs and prescribed drugs are associated with adverse side-effects[112,113]. Furthermore, patients might not always mention the use of OTC drugs to their physician if not explicitly asked. As a consequence of this lack of important information, drug-related problems might go undetected for long periods of time. In a recent survey, 2 594 Swedish persons were asked about their consumption of OTC drugs. Of these, 87% had taken an OTC drug at least once during the past 6 months, the most common of which were analgesics and antipyretics (76%). Age stratifying revealed that persons younger than 60 years purchased OTC drugs more often than older persons (20-39 years: 60.4 %; 40-59 years: 51.6% and ≥ 60 years: 50.1%, respectively)[114]. One probable reason for this distribution is that elderly persons more often take prescribed medication.

A weakness which must be considered when interpreting the results of study II is that adherence to prescription of medication may vary. Depending on the study population, the frequency of medication adherence has been estimated to be approximately 75%[115]. It is possible that similar medication adherence was the case in our study population, thus potentially modifying the impact of PIM on the study outcomes. It is also important to mention that *under-prescription* in elderly patients, *e.g.* essential cardiovascular medication, can also have adverse effects[116] and impact the outcome of surgery.

Another factor having a possible impact on surgery outcome is the use of nutritional supplements, because of their potential interaction with other drugs and adverse side-effects. In study IV, one patient was found to be taking cod liver oil as a source of omega-3. Even if there is no clear evidence of increased risk for bleeding in surgical patients taking omega-3 supplements[117], the patient was recommended to stop intake as long as antiplatelet treatment was prescribed by the surgeon. In a recent review, 23% of surgical patients were using herbal products. Older patients and patients with higher prescription and OTC drug use, preferred to take herbal supplements[118] and many patients might not mention their use of herbal medicine. On the other hand, in a survey of anaesthetists in the UK, 90% reported that they did not routinely ask about herbal medicines, and 82% judged their knowledge of herbal medicines and their implications in patient care as being inadequate[119]. These observations make nutritional supplement an unknown factor during surgery.

The findings in our studies (increased LOS and mortality after surgery in the presence of inappropriate medication, and a trend towards an increased risk for postoperative complications in the presence of polypharmacy) confirm the general necessity of reconsidering patient medication in order to reveal PIM, not only in the preoperative assessment. This is especially important during the perioperative and postoperative periods, since adverse side-effects will probably have an even greater impact at that time. Questions about use of OTC drugs and nutritional supplements and adherence to prescribed drugs should be mandatory and given the same importance.

5.1.4 Patients' experiences

As shown in study III, the impact and investigation of suspected CRC evoke many feelings in the elderly patient´s mind: "How will the cancer affect my life?", "What is going to happen now?" etc. This is a dramatic moment causing insecurity and worry. Lack of information or information insufficiently adapted to the needs of the elderly population leads to feelings of being out of control and being dependent on healthcare professionals. Perception of the patient's emotional status and need of information, and response to this, is essential for the patient's wellbeing. The positive effects of good information extend into the postoperative period where, for example, postoperative pain may be reduced and patient satisfaction enhanced by sufficient preoperative information[120,121]. Decisions on which therapeutic option is most appropriate are sometimes perceived by the patient as being age discrimination as shown in study III. Age is a negative predictor for the employment of chemotherapy[122,123] but surgeons should be aware that patients are seldom objective and have a tendency to interpret things emotionally.

When facing the prospect of surgery, patients usually want to know the routines followed at their hospital, which complications can be expected, how pain and wound care will be handled, and what impact the operation will have on their level of activity[124]. Answers to these questions enable the patient to prepare mentally for surgery and may enhance coping strategies.

5.2 PERIOPERATIVE CONSIDERATIONS

5.2.1 Surgical treatment

Elderly patients are more often operated as emergency cases as shown in study I. An explanation could be that elderly patients are admitted for acute complications caused by an unknown or untreated cancer (regardless of reason). Chronological age, present comorbidity

and patient decisions might be obstacles preventing the referral of elderly cancer patients to specialised care[125], thus contributing to the higher incidence of emergency surgery.

As shown in study I, curative resection was less often performed in older patients when adjusted for TNM stage. Comorbidity is of course one reason not to perform extensive surgery. However, postoperative histopathology in this group generally showed less advanced cancer. Since histopathological staging is dependent on lymph node assessment, and this study showed that fewer lymph nodes were harvested in older patients, one might speculate that this could be a reason for the apparent discrepancy in stage distribution. Furthermore, lymph nodes are subject to the aging process[126], making harvesting more difficult in some cases.

5.2.2 Postoperative complications and mortality

In a recent American study, including 261 886 elective CRC patients, the total rate of postoperative complications was 15.9%[127]. A similar complication rate was observed in study II, regardless of exposure or not to PIM, though only surgical complications were assessed in this study. The 30-day mortality was higher in patients exposed to PIM, even after adjustment for patient- and procedure-specific risk factors. This could reflect the association between PIM and geriatric events such as fall and delirium. These are not reported *per se* in the register but are known to lead to increased mortality[50]. This may be reflected in the findings of study IV, where risk for fall was associated with a slightly increased risk for postoperative complication. None of the remaining CGA assessment variables showed an association with increased risk for complication. On the contrary, risk for malnutrition was associated with a slightly lower risk for complication, possibly due to the transfer of patients to other wards when surgical care was judged to be complete and this may not have been recorded as hospital stay. With certain reservation, a possible explanation for this somewhat contradictory finding could be that dietary intervention in study patients with risk for malnutrition may have broken a negative development regarding weight loss and malnutrition, even though the time to surgery was often short to evaluate the effects of the interventions.

In study IV, delirium was specifically assessed as a postoperative complication. More patients were found to be suffering from delirium than was reported in the SCRCR, though this might be the result of non-detection or non-reporting in the register. There are several patient-specific risk factors for POD in elderly patients undergoing gastrointestinal surgery[51] which we could not confirm in our study, maybe due to possible under-registration and small patient numbers. Risk factors regarding surgery has not been evaluated in study IV but has been

shown previously[51]. The impact of delirium on postoperative outcome is considerable[50] and is thus an important target for improved surgical care.

5.2.3 Length of hospital stay

In an American population-based study including a total of 261 886 patients, the median LOS for patients undergoing CRC surgery, regardless of age, was 6 days. For the patient cohorts ≥75 and ≥85 years, respectively, the LOS increased to >8 days and >12 days, respectively[127] which is comparable to our findings in study II. Frailty is associated with increased postoperative complications and prolonged LOS in surgical patients[128]. Another possible reason for the longer LOS in our study might be the occurrence of geriatric events related to PIM and their subsequent impact on the patients and their surgical care but the register did not provide such information. In study IV we could not show any association between the geriatric assessment variables used and LOS. The trend towards a shorter LOS when risk for malnutrition was detected could again be the result of healthcare logistics with more of these patients being transferred to non-surgical wards not included in the LOS statistics.

In study III, several participants expressed that they were stressed by the thought of being in hospital so short a time. Returning home may well be considered an important milestone, but many patients worry about not being able to cope at home[129]. This stresses the importance of information on what to expect and how to handle symptoms and problems later on. The prospect of follow-up and the possibility to come into contact with specialist care might provide a feeling of safety.

5.2.4 Discharge home

Elderly people are concerned about the impact of their disease on activity status after discharge home. In study III, several participants expressed similar concern as well as the importance of remaining independent in daily life. In study II, more patients with PIM were discharged to other facilities rather than home, prolonging their stay in hospital or rehabilitation centre. Furthermore, data on “home” in the SCRCR do not distinguish between own accommodation with or without assistance or nursing facility, so these results must be interpreted with caution. Furthermore, we had no information about how our patients lived prior to surgery, but we know that use of PIM is higher among nursing home residents[109] which could explain our observations. Another reason could be a higher frequency of postoperative complications in the group using PIM leading to deterioration in function and loss of independency and need for further care in a medical or geriatric ward.

5.2.5 Experiences

An important issue during the time in hospital was food, or rather difficulties in regaining appetite. All patients complained about the quality of the hospital food, regarding it as not particularly conducive to rapid recovery. Nutritional decline is seen during hospitalisation, leading to prolonged LOS[130]. For surgical patients, only male sex was shown to be a risk factors for nutritional decline, whilst for medical patients low admission weight, presence of cancer and two or more diseases, low food intake, food quality, and illness were important[131]. In addition, elderly patients may have difficulties in eating or chewing and this combined with pain or bowel symptoms after surgery can contribute to poor nutritional recovery[132].

Poor information regarding gastrointestinal symptoms after surgery and the importance of maintaining nutrition during the perioperative period has been reported previously[132] and should be a subject for improvement. The prospect of discharge and return to a familiar environment often evokes a feeling of elation, as was the case in study III. At the same time, however, it can be a frightening thought due to having to be alone and cope on their own[129]. Sufficient and comprehensible information alleviates these worries and prepares the patient for this next stage in their recovery.

5.3 POSTOPERATIVE CONSIDERATION

5.3.1 Recovery

Most participants in study III were discharged to a dedicated rehabilitation centre for about five days where group physiotherapy is often included as part of the rehabilitation programme. Some patients declined participation in the rehabilitation programme due to residual problems after surgery, while others perceived the physiotherapy they received to be inappropriate to regain the activity levels present prior to cancer illness and surgery. Taking into account premorbid function and tailoring physiotherapy to the needs of the individual could help patients to adapt during the recovery process, and be more motivated to adhere to the rehabilitation programme.

Apart from prearranged visits to the surgical outpatient department, the responsibility for postoperative care after discharge in Sweden, *e.g.* wound care, is transferred to the primary care system. Previous studies have shown that this system functions poorly, and a consequence of this is that most CRC patients tend to turn to specialist care with their problems[133]. This was certainly the case in study III, where patients described difficulty in getting in contact with their GP; high-lighting the importance of tight contact with the primary care system. Furthermore, practically all CRC patients have a contact nurse at the

surgical out-patient department. However, the possibility to use this resource was not always understood by the participants.

An important theme in Study III was the feeling of insecurity about how to behave after surgery: “Can I shower?”, “Can I exercise?”, “Can I proceed with my former life?”. All participants had to cope with wound self-care and resumption of daily activities. More importantly, however, almost all participants mentioned difficulty in regaining appetite and weight. Nutrition is an important part of the recovery process and patients use weight gain and food intake as a surrogate for well-being and recovery[134]. As shown in study III, information is perceived as inadequate and poorly adapted, but even more relevant is the fact that participants experienced that they were torn between the primary and specialist care systems, since there was no clear division of responsibilities. Discontinuity of care has indeed been described previously, in particular the inadequate transfer of information between specialist and primary care systems, leading to the general impression that the healthcare system functions poorly[135].

Satisfying the patient’s need for information in order to understand and accept the current situation and further events during recovery[136,137] in many ways facilitates acceptance of the situation and their coping with difficulties associated with recovery. In study IV, several patients had questions regarding long-term problems such as nutrition and bowel problems, as well as daily activities such as walking. During this study, we gained the impression that a revisit after 3 months would have been appreciated.

5.3.2 Postoperative follow-up

Although these elderly patients recovered quite well from elective CRC surgery and retained, regained or even improved their preoperative functional status, study IV showed deterioration in health-related quality-of-life up to one year after surgery compared to baseline. HRQoL is a multifactorial indicator of a person’s health status and it is an important factor for all patients, not only the elderly. In a study of 180 surgical CRC patients (mean age 80 years), frail patients reported a lower QoL after surgery than non-frail patients, but the QoL pattern was similar in both groups *i.e*. regained or increased QoL after 3 months but thereafter falling, though still above baseline values (median follow-up 22 months). Postoperative complications have a negative impact on QoL, even after physical recovery, indicating long-lasting psychological impact[138]. Pain, functional and social well-being are factors having an important influence on HRQoL after colon cancer surgery[139]. Study IV gives an overall view of HRQoL: no distinction was made between frail and non-frail patients or between the different items constituting the EQ-5 D. In study III, many participants told felt

torn between the primary and surgical care systems which led to dissatisfaction. Although the EQ-5D is not designed to detect this kind of observation, it is possible that these experiences influenced the quality-of-life of the patients in study IV as well.

Fewer patients were at risk for malnutrition at the 3- and 12-month follow-ups, indicating regained bowel function after a transient decline at 1 month. Weight loss is a catabolic reaction of the body to the stress of a surgical procedure, but it might also have been due to strain after surgery, persisting bowel problems, and being unsure about what food to eat, which was mentioned by several participants in study III. Fall risk showed a temporary improvement at the 1-month follow up, then returning to baseline. One reason could be a review of medication prior to discharge, reinstating drugs associated with an increase in fall risk. No detailed analysis of the various variables used in the fall risk assessment tool was made, but such knowledge could possible provide an explanation for this observation. With the exception of HRQoL and nutrition, all variables assessed during follow-up were comparable to baseline values. Even if study IV was not primarily designed to evaluate the elderly patient's tolerance to and recovery from CRC surgery, it still contributes to our understanding that even elderly and relatively unfit patients often benefit from elective surgery without undue risk.

Elderly patients are often denied more aggressive treatment regimens due to several factors such as age[140] and comorbidity[141], and therefore the effects of treatment may be under- and side-effects overestimated. Another aspect in this discussion is that common parameters assessing treatment outcome may not reflect the preferences of elderly patients. This patient population may prioritise life expectancy, functional status and independency, as well as reduced comorbidity and increased quality of life[142], factors that should be taken into consideration when tailoring treatment to the individual's needs. In view of the increasing and healthier elderly population worldwide, there is clearly room for improvement in the surgical care of this patient population and future research must highlight areas of prioritised interventions.

5.4 STRENGTHS AND LIMITATIONS

5.4.1 Study I

Prospective data from the Swedish National Colon Cancer Register was used. This register has an almost 100% completeness for colon cancer patients operated in Sweden. High validity is ensured by cross-checking medical records and histopathology reports, as wells as continuous validity controls and feedback from research projects. The large number of cases provides a

complete and representative data set but the study was limited to parameters included in the register.

5.4.2 Study II

This study was also based on prospectively reported register data, this time derived from both the SCRCR and the Prescribed Drug Register. The latter was started in 2005 and holds complete information of all medications prescribed in Sweden. It is updated on a monthly basis and has the strength that it can be combined with other registers in a coded context with unique patient identifiers, ensuring patient confidentiality and reliability in the field of research. Since the information available to us was limited to information on prescribed drugs, we had no way of knowing whether the patients indeed used their medications as prescribed or if they used additional over-the-counter drugs such as NSAIDs or medication obtained from providers other than registered pharmacies. The use of non-registered drugs with impact on surgical outcome cannot, therefore, be ruled out.

Since this study investigated the impact of PIM on outcome, the SOS definition was used. We did not have information on whether or not the patient had had a previous diagnosis that justified the use of PIM. Furthermore, adverse side-effects such as delirium or fall are rarely registered in the SCRCR. To overcome this problem we used surrogate variables and endpoints such as length of hospital stay and 30-day postoperative mortality. Several confounders could have influenced these outcomes which is why adjustments for ASA class, age, and tumour stage etc. were made in the multivariate analyses regardless of their impact in the univariate analyses. Subgroup PIM analyses were conducted but could not be used since the numbers were too small and confidence intervals thus became too wide.

5.4.3 Study III

The use of qualitative methods makes a colourful and rich contribution to medical research. Inductive quantitative analysis was chosen to describe how participants experienced a particular subject, *i.e.* the surgical care process and information given. Participants in the study were purposefully selected to ensure varied and rich data on their experiences[143]. On the other hand, this procedure could result in selection bias with the risk of missing participants who could have contributed to the study with other points of view. Patients with dementia and a native language other than Swedish were excluded. By using these exclusion criteria, the experiences of these patient categories were missed. This must be considered when discussing the application of our results to other settings. The last author made the decision that saturation had already been reached after 12 patients, but four more participants were included to ensure saturation. The first and last authors were not part of

the care team, thus limiting the risk of patients feeling obliged to participate or to withhold negative experiences. If questions came up during the interview, the interviewer informed the patient on whom to contact regarding the question.

Recall bias is a limitation that must also be considered, especially in qualitative studies. The interviews took place three to eight months after surgery. This means that the experiences from the preoperative period may have happened even further back in time. Thoughts and feelings that the patients experienced then may well have been forgotten or modified. For example, a negative experience might have remained or even become greater in the participant's memory and this could have had an impact on other experiences.

Loss of non-verbal communication might have influenced the analysis since the first author neither participated nor listened to the interviews due to organisational issues. To balance this shortcoming, all analyses were conducted by or discussed with the last author who performed the interviews. This cooperation was not only part of the learning process but also provided opportunities for discussing various aspects and reflections, and interpretation of the material. This learning process is important since qualitative research is highly dependent on the researcher's personal skill, knowledge and experiences all of which can bias the results.

5.4.4 Study IV

A strength of this study is the approach to generate new hypotheses on potential patient-specific predictive markers, thereby providing clues on how to improve surgical care in elderly CRC patients. However, execution of the study faced some challenges namely limitation to only one dedicated geriatrician and the lack of continuity *i.e*. change of surgical site during the study. This made patient selection and visit coordination difficult, and the calculated number of patients required could not be reached within a reasonable period of time. Furthermore, the time between preoperative assessment and surgery varied widely, implying that it may not be possible to evaluate any positive or negative effects of an intervention on outcome due to the time factor. Furthermore, several patients who were asked to participate thought it was difficult to have to visit to a different doctor or make extra visits to the hospital. This was one of the reasons why the drop-out rate was high, especially when the follow-up only involved a geriatric assessment. Interviews and assessment at home could have increased the inclusion rate and completeness of follow-up. Since there was a suspicion of selection bias due to unfit patients declining participation because of the extra burden, we tested our study cohort for external validity to ensure the generalisability of our results.

As in study III, patients with dementia and a native language other than Swedish were excluded and thereby any deviation in these groups from the rest of the population was missed. Translators and interviews by-proxy could have been used as a complement.

Precision was difficult to reach in the analyses since the number of patients was relatively small, and there was a considerable drop-out during follow-up probably explained by the additional burden of extra visits. We cannot exclude the possibility that drop-out patients might have performed less well in the CGA.

Non-parametric tests were used for the analysis of patient characteristics, since normal distribution could not be assumed. Follow-up assessment results were analysed using parametric tests (paired t-test) according to the convention for this kind of evaluation instruments.

6 CONCLUSIONS

So, what then is the answer to the title of this thesis; can the results of colorectal cancer surgery in elderly patients be improved?

- Study I showed an age-dependent management and surgical treatment of colon cancer to a disadvantage of the older patient group.
- Study II showed that PIM-use at the time of surgery is associated with higher mortality and length of hospital stay after CRC surgery.
- Study III showed that elderly patients with CRC experience a lack of information and indiviualised care before, during and after surgery.
- Study IV showed that elderly CRC patients withstand surgery and recover quite well, and that geriatric assessment, as applied in this study, could not predict those patients likely to have a poorer outcome after surgery.

Throughout the time we conducted these studies, it became apparent that CRC surgery in elderly patients is much safer than is generally believed, which is comforting. But there are several issues that have come to light in this thesis that could be the target of future work aimed at minimising the impact of CRC surgery on elderly patients.

As always, even the best intentions and benefits must be balanced against the cost in terms of resources and time but…. Yes, there is much room for improvement and I look forward to playing a part in that process.

7 SAMMANFATTNING PÅ SVENSKA

Tarmcancer (kolorektalcancer, CRC) är en av de vanligaste cancerformerna med cirka 6400 nydiagnostiserade patienter årligen i Sverige. Av dessa är 44 % 75 år och äldre när de får sin diagnos. Att kirurgiskt avlägsna cancern är den viktigaste botande behandlingen. En allt äldre befolkning innebär också att antalet potentiella kandidater för kirurgi i denna patientgrupp växer. Åldrandet medför en risk för sämre kirurgiska resultat på grund av samsjuklighet, nedsatt funktionsförmåga och minskad tolerans mot yttre stress. Syftet med denna avhandling är att, ur ett helhetsperspektiv, belysa olika aspekter i vården av patienter som är 75 år och äldre och genomgår tarmcancerkirurgi samt att identifiera potentiella problem och förbättringsområden. Fyra studier har genomförts i detta syfte.

Studie I: I denna populationsbaserade epidemiologiska studie, baserad på registerdata, jämfördes 6 141 patienter, 75 år och äldre, med 6 818 yngre patienter med avseende på utredning och behandling av tjocktarmscancer. Resultaten visar att rutinmässig behandling av patienter med tjocktarmscancer är åldersberoende. Patienter i åldern 75 år och äldre var ofta mindre komplett utredda och diskuterades mer sällan på multidisciplinära teamkonferenser före operationen. Dessutom genomgick färre äldre patienter botande kirurgisk behandling när resultaten justerades för cancerstadium.

Studie II: Denna populationsbaserade epidemiologiska studie använde registerdata från 7 279 patienter, 75 år och äldre, som genomgick opertion för tjock- och ändtarmscancer. Patienterna granskades med avseende på förekomst av utskriven – och därmed förmodat använd – potentiellt olämplig medicinering (PIM) vid operationstillfället och dess effekt på dödligheten efter operationen och längden på sjukhusvistelsen. 1 641 patienter hade åtminstone en PIM enligt Socialstyrelsens ”Indikatorer för god läkemedelsterapi hos äldre”. Dessa jämfördes med de som inte hade fått någon PIM utskriven. Resultaten visar ett signifikant samband mellan ökad dödlighet efter kirurgi och förlängd sjukhusvistelse om patienterna använde PIM vid tidpunkten för operationen, även när resultaten justerades för annan samtidig sjukdom.

Studie III: I denna kvalitativa studie intervjuades 16 patienter som var 75 år och äldre och nyligen opererade för sin tjock- och ändtarmscancer vid Karolinska Universitetssjukhuset. Deltagarna intervjuades angående sina upplevelser av vård och information före, under och efter operationen. Studien använde sig av semistrukturerade intervjuer som utvärderades med induktiv innehållsanalys. Resultaten visade att känslan av utsatthet var uppenbar när deltagarna upplevde att de hade fått bristfällig information om sin cancer och den planerade behandlingen samt vad detta skulle betyda för deras dagliga liv och förmågan att klara sig själva. Osäkerhet, förlust av kontroll och känslan av utsatthet var också uppenbar under sjukhusvistelsen om deltagarna uppfattade sin omgivning som störande och oroväckande.

Behovet av stöd och funderingar inför framtiden samt ovisshet kring hur livet blir efter utskrivningen ledde till ökad oro och en känsla av sårbarhet. Under rehabiliteringen saknade flera deltagare en mer individ-anpassad rehabilitering vilket ledde till en känsla av besvikelse. Svårigheter att återfå aptit och en fungerande nutrition var påtagliga efter operationen och utgjorde ett stort hinder för återhämtningen. Utöver detta upplevde deltagarna en oklar ansvarsfördelning mellan primärvården och kirurgklinken, vilket återigen ledde till ökad oro samt enupplevelse av sårbarhet och besvikelse.

Studie IV: I denna prospektiva studie observerades 49 patienter, 75 år och äldre, som planerades för kirurgi på grund av misstanke om tjock- eller ändtarmscancer på Karolinska Universitetssjukhuset mellan 2010-2016. De genomgick före operation en omfattande geriatrisk bedömning (CGA), undersöktes för förvirring efter operation och följdes upp med CGA vid 1, 3 och 12 månader. Potentiella samband mellan utfallen av de individuella bedömningsinstrumenten och komplikationer efter operation samt vårdtid efter kirurgi analyserades. Resultaten visade dock inget samband mellan de använda instrumenten och vare sig komplikationer efter kirurgin eller vårdtiden. I allmänhet tolererade patienterna kirurgin väl och återvann sina ursprungliga funktionsförmågor under uppföljningstiden med undantag av den hälsorelaterade livskvaliteten, vilken var betydligt lägre ännu efter 3 och 12 månader.

Slutsats

Äldre patienter som opereras för tjock- och ändtarmscancer ökar i antal med en åldrande befolkning. Denna avhandling visar att dessa patienter är kapabla att återhämta sig från planerad kirurgi och bör därmed kunna dra nytta av att bedömas för kirurgisk behandling i större utsträckning. Avhandlingen visar även att det finns åldersberoende skillnader i utredningen och behandlingen av tjock- och ändtarmscancer till nackdel för äldre patienter. Bättre metoder behövs för att kunna anpassa cancervården till de speciella behoven i denna patientgrupp. Även om vi inte kunde påvisa ett samband mellan geriatrisk bedömning och resultatet efter operation, tror vi fortfarande att äldre patienter kan dra nytta av att en geriatrisk bedömning, inkluderande läkemedelsöversyn, för att optimeras innan operationen. En viktig del av detta bör även vara att i större utsträckning diskutera äldre patienter i multidisciplinära teamkonferenser för att identifiera riskpatienter och ytterligare förbättra vården vid tjock- och ändtarmscancer för denna patientgrupp.

8 ZUSAMMENFASSUNG

Darmkrebs (kolorektales Karzinom, CRC) ist eine der häufigsten Krebserkrankungen weltweit. In Schweden werden jedes Jahr über 6.400 neue Patienten diagnostiziert, wobei fast die Hälfte 75 Jahre und älter sind. Die chirurgische Entfernung des Tumors ist eine der wichtigsten Behandlungsstrategien, die zur Heilung führen kann, vor allem in früheren Krebsstadien. Mit einer alternden Bevölkerung steigt die Zahl der möglichen Kandidaten für eine Operation in dieser Population, allerding erhöht das Alter auch das Risiko von schlechteren Ergebnisse nach der Operation auf Grund von Komorbidität, eingeschränkter körperlicher Beeinträchtigung Funktion und geringerer Toleranz gegenüber Stress, wie eine Operation ihn hervorrufen kann. Das Ziel dieser Doktorarbeit ist es, verschiedene Aspekte der Versorgung von älteren chirurgischen Darmkrebspatienten hervorzuheben, und auf diese Weise mögliche Probleme und Verbesserungsmöglichkeiten zu identifizieren.

Studie I: In dieser populationsbasierten epidemiologischen Studie, die auf Registerinformation basiert, wurden 6 141 ältere Patienten (≥75 Jahre) mit 6 818 jüngeren Patienten verglichen, mit Schwerpunkt auf die Diagnostik und Therapie von Darmkrebs. Die Ergebnisse zeigen, dass die Routine-Behandlung von Patienten mit Darmkrebs altersabhängig Unterschiede aufweist: Patienten ≥ 75 Jahre wurden seltener vollständig untersucht und in einer multidisziplinären Teamkonferenz vor der Operation ausgewertet als jüngere Patienten. Darüber hinaus erhielten weniger ältere Patienten eine kurative Operation, wenn die Ergebnisse für unterschiedliche Krebsstadien angepasst wurden.

Studie II: Diese populationsbasierte epidemiologische Studie verglich anhand von Registerdaten 7 279 Darmkrebspatienten ≥75 Jahren auf die Verwendung von potenziell inadäquater Medikation (PIM) für Ältere zum Zeitpunkt ihrer Operation. Von diesen hatten 1 641 Patienten mindestens ein PIM, 5 368 hatten keine PIM. Die Ergebnisse zeigten einen signifikanten Zusammenhang zwischen einer erhöhten Sterblichkeit und längerem Krankenhausaufenthalt nach der Operation bei den Patienten mit PIM. Dieser Unterschied war auch immer noch deutlich, wenn die Ergebnisse für Begleiterkrankungen korrigiert wurden.

Studie III: In dieser qualitativen Studie wurden 16 Darmkrebspatienten ≥ 75 Jahre kurz nach ihrer Operation zu ihren Erfahrungen mit dem Gesundheitswesen und erhaltener Informationen vor, während und nach der Operation befragt. Die Studie verwendete halbstrukturierte Interviews, die durch induktive Inhaltsanalysen ausgewertet wurden. Die Teilnehmer empfanden Verletzlichkeit und Unsicherheit, wenn sie das Gefühl hatten, nicht genügend Informationen über ihre Krebserkrankungen, und die geplante Behandlung zu erhalten und was dieses für ihr tägliches Leben bedeuten würde. Unsicherheit, Kontrollverlust

und das Gefühl des Ausgeliefertseins wurde während des Krankenhausaufenthalts empfunden, wenn die Umgebung als störend und stressig aufgefasst wurde. Der Mangel an Unterstützung und Zuspruch, Bedenken über die Zukunft und Überlegungen, wie das Leben nach der Entlassung wird, führte zu Sorge, Unsicherheit und dem Gefühl der Verletzbarkeit. Während der Rehabilitation waren mehrere Teilnehmer enttäuscht, dass die Rehabilitation nicht individuell zugeschnitten war. Probleme, den Appetit wiederzuerlangen und eine gut funktionierende Ernährung nach der Operation wurde als großes Hindernis während der Genesungsphase empfunden. Darüber hinaus nahmen die Teilnehmer eine unklare Verantwortung zwischen dem Hausarzt und der chirurgischen Klinik wahr, was zu Sorgen, dem Gefühl des Alleingelassenseins und Frustration führte.

Studie IV: In dieser prospektiven Studie wurden 49 Patienten ≥75 Jahre über einen Zeitraum von einem Jahr untersucht, die auf Grund des Verdachtes auf Darmkrebs am Karolinska Universitätskrankenhaus zwischen 2010-2016 operiert wurden. Diese wurden vor der Operation einem umfassenden geriatrischen Assessment (CGA) unterzogen, nach der Operation auf postoperatives Delir gescreent und erneut nach 1, 3 und 12 Monaten mit einem CGA untersucht. Die Resultate wurden auf einen möglichen Zusammenhang zwischen den Ergebnissen der einzelnen Bewertungsinstrumente, Komplikationen nach der Operation und der Länge des Krankenhausaufenthalts analysiert. Dies war nicht der Fall. Im Allgemeinen tolerierten die Patienten die Operation gut und gewannen im Großen und Ganzen ihre funktionellen Fähigkeiten unter dem folgenden Jahr zurück. Nur die gesundheitsbezogene Lebensqualität war während des Folgejahres deutlich niedriger.

Schlussfolgerung

Diese Doktorarbeit zeigt, dass Patienten über 75 Jahre sich gut von ihrer Darmkrebsoperation erholen können, doch gibt es Gebiete, die noch verbessert werden können. Bei der Diagnostik und Behandlung von Darmkrebs wurden, zum Nachteil für ältere Patienten, altersabhängige Unterschiede festgestellt. Die Anwesenheit von PIM zum Zeitpunkt der Operation ist mit einem erhöhten Risiko für Komplikationen und längerem Aufenthalt im Krankenhaus verbunden. Obwohl wir keine Beziehung zwischen einem Assessment und das Ergebnis nach der Operation zeigen konnten, glauben wir dennoch, das ein Assessment vor der Operation gebrechliche ältere Menschen identifizieren kann, und die weitere Behandlung und Pflege an die besonderen Bedürfnisse dieser Gruppe von Patienten angepasst werden kann. Diese individuelle Anpassung, vor allem in der Rehabilitationszeit, wurde auch von den Patienten vermisst. Sehr wichtig ist auch die ausführliche und angepasste Aufklärung der Patienten, was einen positiven Einfluss auf das Wohlbefinden der Patienten haben kann und die Zeit der Erholung erleichtern kann.

9 ACKNOWLEDGEMENTS

First and foremost I wish to thank all participating patients in studies III and IV. Without you, I would not have had the possibility to show the problems you encountered when becoming colorectal cancer patients.

Second, I wish to express my gratitude to my supervisors after these 7 years together:

Ulf Gunnarsson, main supervisor – you were extremely dedicated and always helped me to see the bright side of researching when dark clouds loomed above (often when miscalculations turned up in one or other excel-file). The idea of combining geriatrics with surgery was and still is intriguing. It closed the loop in my medical studies, bringing together my own speciality with that I was really interested in – standing in the operation room, holding the operation field clear for the surgeon or maybe being allowed to take care of some minor bleeding (which was considered to be a great honour for students). I really will miss the evenings in your small apartment drinking apple juice from Lejsta.

Monika Egenvall, co-supervisor – your eagle eyes were as invaluable as your ability to direct the attention to practical and essential details during meetings and research discussions. You helped with the task to always trying to answer the questions of How? and Why?

Inga Klarin, co-supervisor – your support throughout the years was very important for me – from the beginning when I came to Sweden and started to work as a physician and later as a resident and specialist. Your decision to be on board of my PhD-student time was a very securing thought. Thanks! Sorry, but there will be more tears…

Johan Lökk, co-supervisor – for your "old school"- enthusiasm and trust in me and the subject of my research, and for providing an excellent work environment during this thesis.

Anders Wennlund, my mentor and colleague – for your kind support over the years. Your ability to see the good in every person and our personal and ethical discussions and talks are really inspiring for me.

Marie Iwarzon, co-supervisor during study III – for introducing me to the world of qualitative research. This is the jigsaw piece I have always missed in quantitative research: patients are more than just numbers, p-values and odds ratios. They have stories and feelings that put a face to the person behind a diagnosis. Qualitative research is equally as important in increasing our knowledge as quantitative research.

My (former and present) colleagues at the Geriatric Department at Karolinska University Hospital Huddinge for their support and – (I hope!) – understanding over the years, but especially during the last 6 months. Special thanks to **Frida Göthe** and **Johan Lundberg** for their standing in during study IV.

The administrators **Linda Olsson** at Umeå University, **Annette Karlsson** and **Catarina Cleveson** at NVS, Karolinska Institutet and **Malin Björck** at the Geriatric Department at Karolinska University Hospital Huddinge. You saved my life several times by providing forms and certificates with short notice and by helping me through the administrative jungle.

The **colorectal nurses** at the Huddinge and Solna surgical outpatient departments: in particular Marie and Ingela (Huddinge), and Madelene, Erika, Hanna and Sima (Solna).

Thyra Löwenmark for help with statistics, and **Peter Cox** for linguistic support throughout this thesis.

My research fellows from CLISTER – for your feedback which always forced me to find better explanations for issues and problems which were clear to me as a geriatrician but maybe not to others. Thank you, **Malin Mörner**, for passing on information about half-time and disputation (always good to know someone who already did this…)

My dear friends – both in Sweden and in Germany: thank you for being there for me and my family. Your support, distraction, laughter and encouragement but also interest in what I really was doing here, have all been so important for me. **Vera und Olli** – for your friendship over the years (can you believe, it's already 20 years!). **Claudia** – for the girls' weeks only….Viel Glück mit deiner Doktorarbeit!

Ganz lieben Dank auch an meine Familie für Eure Unterstützung, Hilfe und alle warmen Gedanken. Allen voran **Mutti, Matthias und Ines** – ich habe Euch lieb!

Most important of all –**Nele, Ida and Magnus**, thanks for all of your support, love, help, encouragement – hela rubbet! Utan dig, Magnus, hade det här arbetet inte funnits på det sättet! Jag älskar er! Bordet (och golvet) blir åter fristad för alla pysselgrejer istället för massor med ”viktiga” papper ☺ Förlåt, Nele, att det inte fick vara en regnbåge i mammas bok, men nu har jag tid för regnbågar igen.

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11 APPENDIX

Interview guide study III

BEFORE THE OPERATION

What were you thinking whilst on our way to the hospital? How did you get to the hospital? Was a relative / family member with you?

Please tell me what you thought and felt when receiving your diagnosis?

Please tell me what happened next after you received your diagnosis?

How was your care before surgery when it comes to any other diseases and medication taken to treat them? (E.g. diabetes, heart diseases, lung diseases, infections .....)

Did you at any time experience that someone asked the question what your home situation looked like?

(If Yes, Who was it? And when was the question asked? In what way was the question asked?)

Regarding other relatives/family members, can you please tell me about your experience how they were given information about what would happen? (Continued care and treatment, by whom, when.)

Please tell me about the information you got prior to surgery? (If it was good - what was good?)

In what way did you receive the information? (In writing, orally, by whom, when, who was with you.)

Can you please tell me about the content of the received information? (Surgery, procedures, preparations, any pain-pain relief, nausea, treatment, following events , any ostomy care, rehabilitation, nutrition, access to aftercare in the home etc., assistance from the municipality, impact on the psycho-social life, socializing with relatives, sexual functionality)

In your opinion, did you receive sufficient information about what would happen before surgery? (If not, what are you missing?)

How did you experience the information about what would happen during the hospital stay?

How has the information helped you?

Would you have preferred the information to be given in any other way? (And if so, in what way?)

Did you miss something? (If so, what?)

Can you please tell me how you experienced the information from the different professions? (Where they repeating the same information, and if so, was this good or bad, what was it that was good or bad)

Do you feel that you have been listened to?

DURING THE HOSPITAL STAY

What did you think and feel during the hospital stay?

What happened next? Can you please tell me how you experienced what it was like during the time of hospitalisation?

Did you experience that the information you received during the hospital stay was adequate? (Regarding surgery, procedures, preparations, any pain-pain relief, nausea, stool, treatment, following events , any ostomy care, rehabilitation.)

If not, tell me what you missed?

RELATED TO DISCHARGE

Please tell me about your experiences related to your discharge!

Can you please tell me how you perceived the information you received in connection with the discharge? (By whom did you get the information, what was it about, pain-pain relief, nausea, treatment, , following events , any ostomy care, rehabilitation, nutrition, access to aftercare in the home etc. , assistance from the municipality, impact on the psycho-social life; socializing with relatives, sexual functionality)

Please tell me about any other diseases and medications in connection with your discharge? (e.*g.* Diabetes, heart diseases, lung diseases, infections, were there any changes and if so, what changes)

I would also be interested in how you lived/live after discharge? (Has anything changed, adapted housing, return to the same accommodation as before?)

When it comes to your relatives who gave them the information they needed, and that you wanted them to get? (Regarding continued care and treatment.)

When you think back, what would you say have been useful? Valuable? In what way? What have you missed? What can be done better?

The ideal care, how would you describe it? (Set against how the older person experienced it was)

Have you been asked about how you are feeling? (Pre/post operatively.)

In what way do you experience that the information received has helped you?

Is there anything that you would like to add that was not discussed during the conversation?

May I get back to you if I have additional questions?